ACTA RADIOLOGICA
EDITA IUSSU SOCIETATUM RADIOLOGICARUM
DANIAE, FENNIAE, NORVEGIAE, ET SUECIAE

VOL. 38 SEPTEMBER 1952 FASC. 3

A PHOTOMETER FOR DETERMINATION OF EXPOSURE TIME IN RADIOGRAPHY

by

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One of the greatest difficulties in practising good roentgen technique is to obtain sufficient experience in choosing the correct times of exposure. The patients and the problems vary indefinitely, and even the most able and experienced radiographer will not always be able to determine the correct exposure time which always constitutes a considerable difficulty for the beginner as well as for the less able radiographer.

The conditions of radiography in many ways resemble those of ordinary photography. The photographer, however, may obtain the assistance of photo-electric exposure meters which, when directed towards a given object produce a scale deflection corresponding to the amount of light falling upon it. From this reading the correct time of exposure corresponding to the various diaphragm settings may be calculated.

In our opinion a similar instrument for use in radiography would prove most useful and with this in mind the photometer to be described has been designed.

Our purpose in the construction of the photometer has been the creation of a device which, when the film is substituted with a suitable photocell, registers an effect corresponding to the density of the film through the deflection of a pointer on a measuring scale during the exposure.

In order to secure a constant relationship between film density and scale deflection we have endeavoured to imitate in the individual elements of the apparatus the events taking place during an ordinary photographic exposure; we have also striven to free ourselves from the manifold and complicated factors which might produce uncertainty and necessitate corrections.

Submitted for publication, Febr. 5, 1952.

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During the trial exposure:

1) The same kV, MA sec., and light-path are used as during the photographic exposure.

2) The same conversion of the roentgen radiation into visible light takes place as that which occurs in the intensifying screen, so that the non-linearity and the kV dependence are equal.

3) Furthermore, a spectral sensitivity range of the photo-cell as near that of the roentgen film as possible has been chosen and an endeavour to reproduce the so-called Schwarzschild-effect through integration has been made.

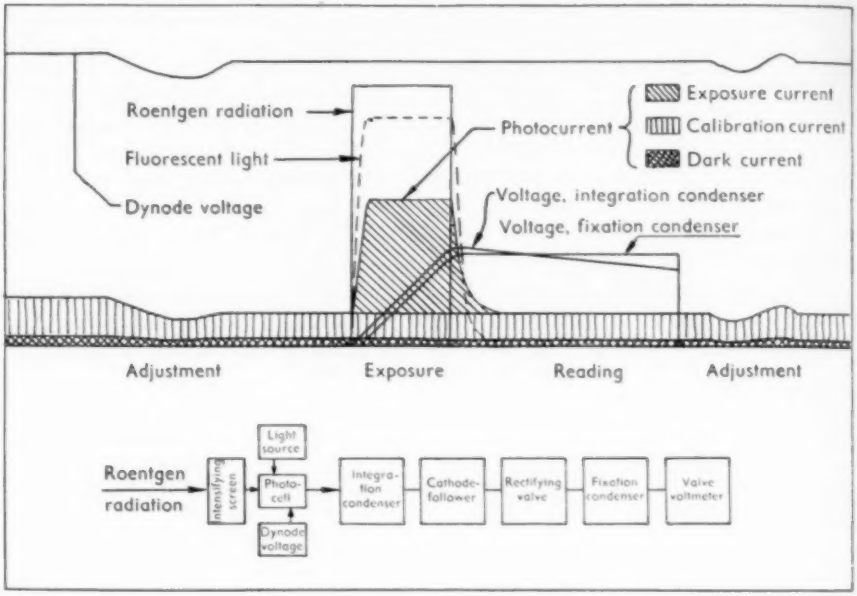

Fig. 1.

The apparatus is shown schematically in Fig. 1: an intensifying screen is energized by the incoming roentgen radiation; the resulting fluorescent light is caught by a photo-cell and the released photo-current charges an integration condenser. The voltage produced in this way is picked up by a cathode-follower coupling and led through a diode to a valve voltmeter. Across the input circuit of the latter a condenser is placed and fixes the voltage transmitted through the diode, so that the peak-voltage of the integration condenser — corresponding to the amount of light — may be held until a reading of the valve voltmeter has been

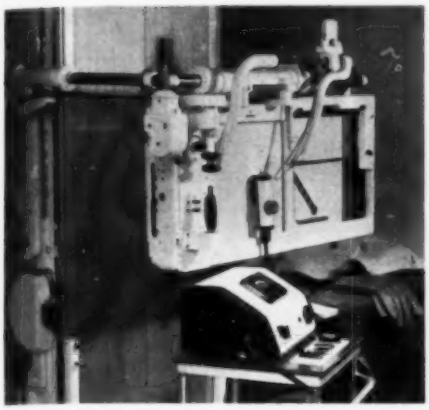

Fig. 2. The photocell attached by suction to the screen with the photometer beneath.

Fig. 3. The radiation penetrates the film into the photocell. The exposure is interrupted when a suitable point on the scale is reached. (Only for exposure times longer than 1 sec.)

taken. The amounts of light at the disposal of the photocell are very small. We have therefore chosen a multiplier photo-cell which, in spite of certain drawbacks, is very suitable for the integration of the photo-current.

As the sensitivity of photocells of this type is subject to very strong fluctuations, a light source illuminating the photo-cathode with a constant but faint, light-intensity (about 0.1 lux) has been utilized for standardization.

The sensitivity of the photo-cell is adjusted (through regulation of the dynode voltage), until at a given light intensity an electron current (photo-current + dark-current) of 1 μA is generated; the voltage over the cathode-follower will then bring the pointer of the valve voltmeter into the zero position.

The procedure is as follows: The left knob is turned to 'Adjustment' (the deflection of the measuring instrument disappears, the fixation and integration condensers are discharged and switched off, and the diode is short-circuited); by turning the right knob (controlling the dynode voltage of the photocell) the pointer of the measuring instrument is placed

on '0'. The left knob is then turned to 'Exposure' and the apparatus is ready for measurement.

The variations in the elements of the apparatus during adjustment, exposure and measurement are shown in Fig. 1.

In practise the photometer is employed as follows:

During fluoroscopy the photocell is placed in the most suitable position on the screen, *i. e.* the region where the centre of the film is to lie. A trial exposure is made and from the scale-reading of the photometer the correct time of exposure is determined (Fig. 2).

For ordinary radiography without screening a photocell containing a built-in fluorescent screen is placed where the centre of the film will lie, a trial exposure made and the time of exposure determinated as above.

With exposure times longer than 1 sec., one may place a non-screen film on the daylight photocell and expose until the scale-needle reaches the correct point. A similar technique may be used when working with intensifying screens and casettes. (Fig. 3.)

The photometer is so adjusted that the scale-reading 0.75 or 0.5 by trialexposure with a Cawo-screen corresponds to the ideal exposure with an intensifying screen of medium speed. We have used Kodak and Ilford films exclusively.

The photometer has been so calibrated that when reading 1 corresponds say to 0.1 sec., reading 2 will correspond to 0.2 sec., 3 to 0.3 sec., and so on, provided all other factors are constant.

The photometer has been in use at the Copenhagen County Hospital for the past 6 months. The results of the measurements have been constant and extremely reliable. We have always obtained excellent films with exposure times corresponding to scale-reading 1, even with thick-set patients. The photometer measures without difficulty exposure times up to 7 seconds.

We have studied the influence of voltage on the measurements, and with intensifying screens these have proved to be reliable, at any rate at voltages ranging from 55 to 125 kV.

Disregarding a few minor individual variations, the screens have proved to be surprisingly uniform; furthermore, we tried an old screen, which gave a reading of 0.50 corresponding to 1 for the newer screens.

The reliability of the photometer makes it widely applicable for instructional purposes. The difference in speed between the various intensifying screens (fine, medium and coarse grain) is easily demonstrated. Furthermore, a study of the following factors is possible: The sensitivity of the film, the luminous intensity of the screens, the output of the roentgen units, the prolongation factor for grids, the influence of the 'Square Law' and finally the penetration factor of various objects under the most

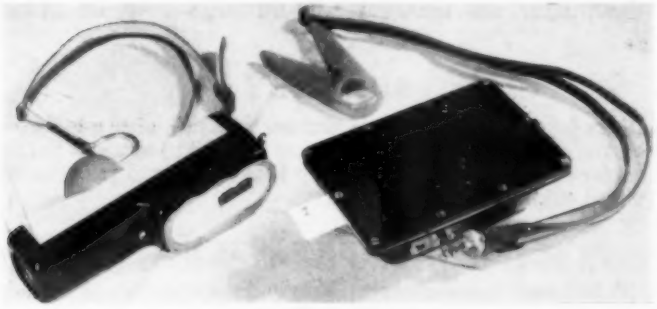

Fig. 4. Two types of photocells. The left for fluoroscopic work, the right for use in daylight; different screens can be placed in these types of photocells.

complex conditions, which is the original and basic purpose of the apparatus.

The sensitivity of the apparatus may be regulated should the speed of the film or the screens be changed. Though the development of the apparatus for practical use has only recently been completed, we feel justified in enumerating the fields in which the photometer may be particularly useful:

Studies of the biliary tract, for which purpose the technique cannot be too precise. Lateral views of the chest. Examination of stout patients generally. Pregnancy (during the first months by reason of the exact technique required, during the latter months by reason of the increased size of the patient). All acute abdominal conditions for which the photometer should prove especially useful to younger members of the staff on duty. Furthermore, a single photometric determination of each patient at the commencement of the examination of the gastrointestinal and urinary tracts is of considerable assistance. In radiographing children the photometer will often be found to be most valuable, and the same applies to all special fluoroscopical examinations in which special projections are used.

The photometer is invaluable when a new roentgen unit is brought into use as well as for the use of personnel with lack of experience.

The application of the photometer requires an extra exposure and therefore naturally increased slightly the wear on the roentgen tubes; however, this drawback is more than compensated for by avoiding overexposures and saving of time and film. The saving of time is brought about by the fact that one may proceed with a difficult examination without awaiting the development of the first film. By the application

of the photometer the necessary information may be obtained immediately.

SUMMARY

The authors describe a new roentgen photometer which, after a test excitation, indicates by means of a pointer the exposure time required to obtain a suitable density. Special types for fluoroscopy and radiography have been developed. The value of the device is pointed out.

ZUSAMMENFASSUNG

Die Verf. beschreiben einen neuen Röntgenphotometer. Dieser gibt, nach einer Testerregung, mit Hilfe eines Zeigers die Exponierungszeit an, die zur Erzeugung der passende Dichte erforderlich ist. Spezialtypen für Durchleuchtung und für übliche Röntgenphotographie sind konstruiert worden. Der Wert des Photometers wird hervorgehoben.

RÉSUMÉ

Les auteurs décrivent un nouveau photomètre radiologique qui, après étalonnage, indique par une aiguille le temps de pose nécessaire pour obtenir une densité convenable. Ils ont fait construire des appareils spéciaux pour la radioscopie et pour la radiographie et insistent sur leur intérêt.

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CONTRAST INVESTIGATIONS ON THE EFFECT OF CAROTID-JUGULAR FISTULAE IN CHILDREN WITH CEREBRAL LESIONS

by

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BECK et al. in 1949 published particulars of a method by which arterial blood might be supplied to the cerebral cortex via venous channels (revascularisation) in children with brain lesions with a supposedly inadequate cerebral blood supply.

By means of an anastomosis between the common carotid artery and the internal jugular vein with ligature of the vein below the anastomosis, an attempt was made to force the arterial blood to flow in a retrograde direction via the transverse sinus and the superior sagittal sinus up into the cortical veins. In this way it was hoped to obtain an increased supply of arterial blood to the capillaries in the cerebral cortex. BECK et al. stated a year later that clinical improvement was achieved in approximately 33 % of their cases while complications occurred in approximately 15 %.

The value of the method was investigated at the Children's Hospital, Gothenburg, in 14 cases. In association with these cases, certain angiographic examinations were carried out, some before operation in order to judge the anatomic and physiologic conditions for operation, and some after operation in order to obtain, if possible, an impression of the changes which might have occurred in the circulation.

I. Contrast investigations before carotid-jugular anastomosis:

A. Direct sinography via the superior sagittal sinus. 14 cases.
B. Indirect or retrograde sinography

Submitted for publication, Jan. 14, 1952.

1) by introduction of a tube into the jugular bulb, 1 case.
2) by percutaneous puncture of the jugular bulb, 1 case.

C. Bilateral carotid angiography, 14 cases.

A. *Direct Sinography.* It has long been known that the cerebral and venous drainage channels show numerous variations. Anatomic investigations carried out to date favour a certain right-sided predominance, *i. e.* the greater part of the blood leaves the skull via the right transverse sinus and jugular vein, but the figures of the frequency vary greatly. Thus, WOODHALL found a right-sided predominance in 39 %, EDWARDS in 36 %, LENHOSSEK in 58 % and FRENCKNER in 47 % of cases. As BECK et al. considered that the blood from the cerebral cortex mainly flows downwards from the superior sagittal sinus via the right transverse sinus and internal jugular vein, they made the anastomosis in all their cases on the right side. As, in an individual case, it cannot be known with certainty on which side the drainage channels from the superior sagittal sinus are best developed, we thought it necessary to obtain information about this prior to operation in order to determine on which side the anastomosis should be performed.

Studies with contrast media on the superior sagittal sinus and its drainage channels have thus been carried out pre-operatively in all cases.

In many cases, it is true, quite good filling of the superior sagittal sinus with the contrast medium is obtained during ordinary cerebral angiography but the filling of the transverse sinus and the internal jugular vein is, as a rule, inadequate for the estimation of calibre. We have therefore, used direct injection of the medium into the superior sagittal sinus (direct sinography).

Technique. A hole is drilled over the superior sagittal sinus immediately posterior to the coronal suture. Ten cc. of the contrast medium are injected by direct puncture of the sinus. A film is taken during the injection of the last 4 cc. In order to prolong the usually very rapid drainage and to reduce the rapid dilution of the medium, the foot of the table and consequently the thorax are raised.

On account of the risk of injecting the contrast medium outside the sinus, the technique has however, been modified. Instead of puncturing the superior sagittal sinus, this is opened and a fine polyethylene tube, which is later closed by means of an Olofsson-Heyman needle, is introduced into the lumen; the incision is then sutured and the tube secured to the skin. The injection is performed through the tube. When the examination is completed the tube is withdrawn from the sinus and haemorrhage controlled by means of pressure on the wound and raising of the head.

The film is taken with the patient supine and the tube angled 25 to 30 degrees cranially; from it, it is usually possible to estimate the calibre of both the transverse sinus and the internal jugular vein. In a number of cases a lateral film of the skull was also taken during the injection. It has previously been shown that in investigations of vessels with contrast media consideration should be given to the sedimentation tendency of the media (KJELLBERG). Control examinations were therefore carried out in those cases in which filling of only the transverse sinus on the one side or marked inequality of filling on the two sides was obtained; the head was turned so that the sinus not filled with opaque medium was dependent in order in this way to facilitate a possible passive flow into it. It proved however, that under such conditions the same appearances as before were obtained.

As all investigations were carried out on children avertin anaesthesia was employed, supplemented when necessary with small quantities of ether.

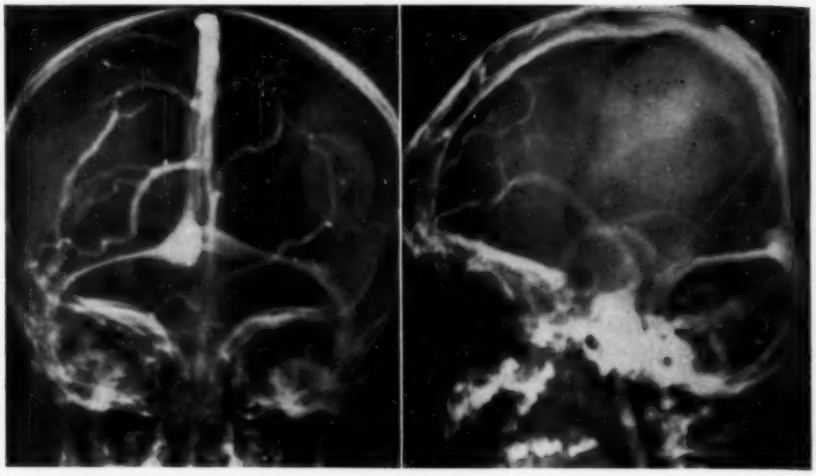
Complications. Complications may arise if the contrast medium be injected outside the sinus. These may consist of generalised epileptiform fits, particularly if the patient be conscious or only lightly anaesthetized. The contrast medium appeared outside the vessel in two cases. One of the patients had no such fits or other abnormal signs but was, however, kept under the anaesthetic until all the medium had been absorbed, which occurred in one and a half hours. There was no sign of injury later. The other patient developed generalised fits, which, however, were abolished by a deepening of the anaesthesia and later the injection of sodium barbitone (0.05 gm $\times$ 2). Two hours later all the contrast medium had disappeared from the brain surface and the fits did not recur. The risk of perforating the sinus has, however, practically disappeared as the sinus is not punctured, but a polyethylene tube inserted. Thrombosis or other injury never occurred in our series.

Results. Direct sinography has been used in 14 cases to date. The cases in the material have been grouped with regard to the clinical problems, *i. e.* the calibres of the drainage channels, connected with the superior sagittal sinus as follows:

Table 1

Bilateral symmetrical drainage	5
Right-sided predominance	1
Left-sided predominance	5
Unilateral, right	2
Unilateral, left	1

As is apparent from the distribution in the table, a principally right-sided drainage from the superior sagittal sinus cannot just be assumed.



a. b.

Fig. 1. a. Sinography: Injection into the superior sagittal sinus against the stream; bilateral symmetrical outflow. Note the filling of the cortical venous system.
b. The same case: Lateral view.

(Figs. 1 a & b, 2, 3 and 4.) Also in cases of predominance of the drainage from one or other side, the sinogram has shown in some cases such a significant difference in calibre between the transverse sinuses that the drainage could practically be classified as unilateral. In accordance with these findings, the choice of side for the anastomosis should be deliberated and it is perfectly clear that in 6 cases it would have been incorrect to form the anastomosis on the right side. In one of these cases (14) (see Fig. 4), it would have been anatomically impossible to have introduced arterial blood from the right internal jugular vein via the transverse sinus into the superior sagittal sinus.

B. *Indirect or retrograde sinography* has been carried out chiefly in order to see how far the contrast medium could be forced up into the sinus system in a retrograde direction — in the same direction as the arterial blood after the formation of the fistula.

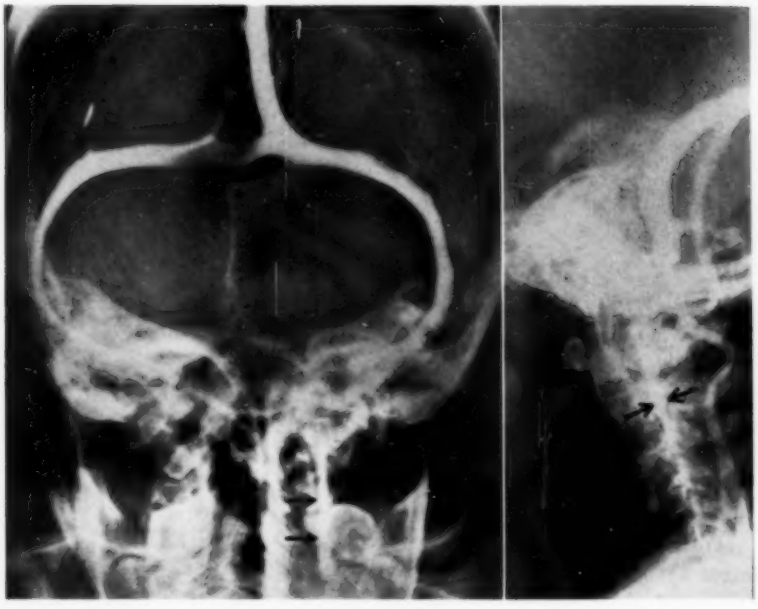
Retrograde sinography was employed pre-operatively in two cases in which direct sinography had shown mainly symmetrical drainage.

1) In one of the cases (12) the contrast medium was injected through a polyethylene tube introduced into the bulb of the jugular vein. The latter was clamped below the tube. Filling of the transverse sinus was obtained but none of the contrast medium could be seen in the superior

Fig. 2. Sinography: Marked predominance to the left. Note the different size of the jugular veins.

Fig. 3. Sinography: Injection into the superior sagittal sinus. Unilateral outflow to the right. The head turned to the left to exclude sedimentation.

Fig. 4. Sinography: Injection into the superior sagittal sinus. Unilateral outflow to the left.



a. b.

Fig. 5. a. Sinography: Follow-up study after end-to-side shunt between the external carotid artery and internal jugular vein. Injection into the superior sagittal sinus. No suppressing effect on the drainage. Outflow as before. Simultaneous filling of parts of the vertebral plexus b., which could not be visualized before the operation. Compare Fig. 2.

sagittal sinus or in the transverse sinus of the other side. The injection was performed by hand with the greatest possible force.

2) In the other case (13) the bulb of the internal jugular vein was percutaneously punctured with the point of the needle according to the method of MEYERSSON, HALLORAN and HILL, and modified by GIBBS. The contrast medium flowed into the vertebral plexus; none passed into the sinus system.

Thus, in neither of these cases could the medium be successfully forced up into the superior sagittal sinus.

C. *Bilateral cerebral angiography* via the internal carotid artery was carried out pre-operatively in 14 cases, partly in order to obtain a basic picture with which the post-operative cerebral angiographies might be compared and partly to exclude possible pathologic conditions in the vessels.

Fig. 6. Retrograde sinography: Follow-up examination. Contrast injected in the bulb of the jugular vein. No filling of the transverse sinus. Visualization of the inferior petrosal sinus. Good filling of the vertebral plexus.

Fig. 7. Frontal view. Retrograde sinography after operation. The main part of the contrast went down in the ligated jugular vein and into various veins in the neck.

II. Contrast investigations on the effect of carotid-jugular fistulae.

A. Direct sinography via the superior sagittal sinus. 3 cases.

B. Indirect or retrograde sinography by percutaneous puncture of the jugular bulb. 5 cases.

C. Angiography via the common carotid artery.
   1. In immediate connection with the operation
      (a) without simultaneous clamping of the internal carotid artery. 5 cases.
      (b) with simultaneous clamping of the internal carotid artery. 1 case.
   2. Some weeks after operation. 8 cases.

A. *Direct sinography* with direct injection of the contrast medium into the superior sagittal sinus was carried out some time after operation in order to study the changes which might possibly have occurred in the drainage from the superior sagittal sinus. This was done in three

Fig. 8. Angiography immediately after anastomosis: Injection into the common carotid artery with simultaneous clamping of internal carotid. Filling of the internal jugular vein up to the base of the skull.

cases (6, 7 and 10). In two of the cases (6 and 7) with definite left-sided predominance in the drainage, the bulk of the contrast medium still continued to flow through the left transverse sinus but later went over into the veins of the neck belonging to the vertebral plexus system and which were not filled in the pre-operative direct sinography. (Figs. 5 a and b.) Thus in these cases, left-sided predominance of the drainage was still present despite proximal ligation of the jugular vein and the short-circuited arterial blood stream on the left side.

In the third case (10) in which the drainage was more symmetrical, the distribution to the right and left sides was unchanged after operation but the mastoid emissary vein on the operated side filled with contrast medium.

B. Attempts at *retrograde sinography:* Five cases (1, 10, 11, 12 and 13). In two of the cases (10 and 11) no contrast could be seen in any part of the sinus system but had flowed over into numerous other veins of the neck. In case 12 good contrast filling was obtained of the inferior petrosal sinus up towards the cavernous sinus as well as of the plexus situated on the posterior aspect of the dorsum sellae (Fig. 6).

In case 13, small quantities of the contrast medium were seen in the inferior petrosal sinus with good simultaneous filling of the vertebral plexus. In case 1, some of the contrast entered the transverse sinus while the bulk of it flowed downwards in the ligated jugular vein and passed over into various veins of the neck (Fig. 7).

Thus, at this examination no contrast medium flowed up into the superior sagittal sinus via the route intended, despite the anastomosed

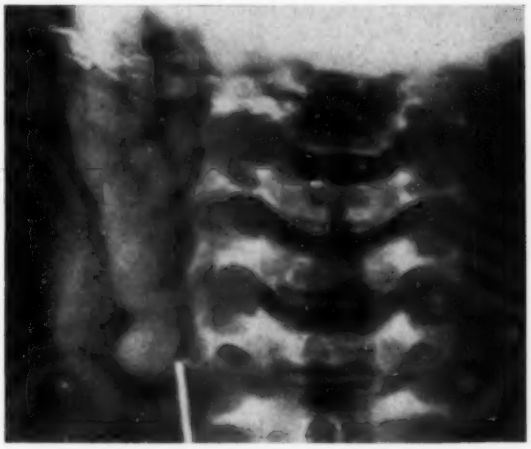


Fig. 9. Angiography via a large common carotid-internal jugular vein fistula: Grossly enlarged jugular vein.

arterial blood stream and the high pressure of injection, but in two of the cases a certain filling of the intracranial venous system was, however, obtained.

C. *Postoperative carotid angiographies* were made in order to study the function of the fistula and possible changes in the angiographic picture in comparison with the pre-operative cerebral condition.

1) In five cases angiography was performed in immediate connection with the fistula formation (4, 8, 9, 12 and 13).

In two of these cases (8 and 9) the route of the contrast medium into the internal jugular vein via the fistula could be verified simultaneously with the filling of the branches of the internal carotid artery, but in neither of these cases could any of the medium be seen in the sinus system. However, in one of the cases (9) very good filling of the internal jugular vein up to the base of the skull was obtained after clamping the internal carotid artery (Fig. 8). No simultaneous filling of any part of the sinus system was evident. In the other cases where no passage of the contrast medium via the fistula could be seen, very good filling of the internal carotid artery and its intracranial branches was obtained, indicating that as a maximum, only a very small quantity of blood had flowed through the fistula into the vein.

In these angiographies during operation, the passage through the fistula is rendered to a certain degree difficult by possible traction on the vessels during the injection.

Retrograde filling of the superior sagittal sinus with contrast medium

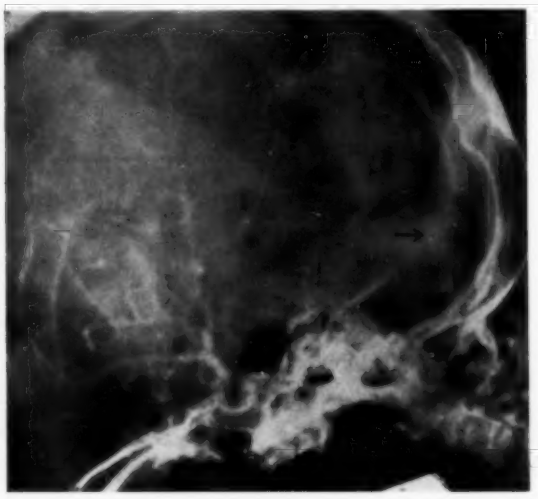


Fig. 10. Follow-up carotid angiography: Good filling of transverse sinus.

in cases in which the medium flowed via the fistula into the internal jugular vein, could also not be obtained in these examinations.

2) In 8 cases angiographies were performed some weeks after the operation. (1, 2, 3, 4, 6, 7, 10 & 14.)

In two of these cases (1 and 2) a rather wide side-to-side anastomosis between the common carotid artery and the internal jugular vein had been performed, with simultaneous ligation of the external carotid artery.

In both of these cases the contrast medium flowed over into a dilated aneurysm-resembling internal jugular vein which could be followed upwards to the base of the skull. (Fig. 9.) No filling of the internal carotid artery and its branches was obtained in these cases — contrary to the results in the remaining cases, in which strikingly good simultaneous filling of the internal carotid artery and its branches was obtained. At re-operation on account of complications no thrombosis of the internal carotid artery was found.

Of the remaining six cases, a patent fistula could be demonstrated radiologically in three cases (4, 6 & 10) by reason of the fact that the contrast medium flowed over into the internal jugular vein. In case 4 the contrast filling extended upwards into the transverse sinus. There was purely unilateral drainage. Angiography in connection with the operation without clamping of the internal carotid artery had also been carried out in this case. No contrast in the internal jugular vein was then visible. (Fig. 10.) In case 5 no contrast could be demonstrated

directly in the jugular vein but the fact that veins in the neck were contrast-filled simultaneously with the common carotid proved that the fistula must have been patent.

In the remaining cases (3, 7 & 14) angiography presented no evidence that the fistula was patent; the contrast medium was visible only in the internal carotid artery. In certain other cases the first part of the external carotid artery was visible but no contrast could be seen in the veins. Minor variations in the degree of contrast filling of the internal carotid artery and its branches in pre- and post-operative angiography can, however, not be considered as certain indications of changes in the circulation.

Discussion

Angiography can naturally give only a rough impression of the circulation as the concentration of the contrast medium must reach a certain level before it becomes visible in the film. For that reason we have supplemented it with regular oxygen analyses of blood samples from the carotid artery, superior sagittal sinus and the contra-lateral jugular vein.

If the short-circuited arterial blood flows up into the superior sagittal sinus, the difference in the oxygen content (Δ 1) between the common carotid artery and the superior sagittal sinus should be less after operation than before.

If, on the other hand, after formation of the fistula, the arterial blood flows directly from the jugular vein via the transverse sinuses into the other jugular vein, the oxygen content must increase, *i. e.* the difference in oxygen content (Δ 2) between the carotid and the contra-lateral jugular vein must decrease.

The results of the oxygen analyses are grouped in the table 2.

A comparison between the roentgen findings and the results of the oxygen analyses reveals strikingly good agreement.

Only in two cases (9, 12) did the oxygen analyses show that arterial blood reached the superior sagittal sinus via the anastomosis. This does, of course, not necessarily imply that this arterial blood in the superior sagittal sinus ever reached the capillary network of the brain. No contrast medium was visible in the sinus system during angiography.

In 3 cases (1, 2 & 9) the oxygen analyses showed direct transference of blood from the one jugular vein to the other. In these cases, direct sinography showed bilateral symmetrical drainage, for which reason the anatomic condition for a direct transference existed. In cases 1 and 2 a broad side-to-side anastomosis between the common carotid artery and the internal jugular vein had been performed, the result of which was a large volume-minute flow through the fistula.

Tab. 2.

Correlation between results of O_2 analyses and Roentgenographic results

Pat.	before shunt values O_2 vol %					after shunt values O_2 vol %					angiographic proof of functioning fistula	filling of some part of sinus system with contrast medium
Nr.	carot.	sinus sagitt. sup.	contra later. jugul.	Δ_1	Δ_2	carot.	sinus sagitt. sup.	contra later. jugul.	Δ_1	Δ_2		
1	—	—	—	—	—	16.8	15.2	11.4	5.4	1.6	+	—
2	—	—	—	—	—	14.7	9.5	14.1	5.2	0.6	+	—
3	15.3	12.1	11.5	3.2	3.8	15.3	12.1	11.5	3.1	3.8	—	—
4	15.2	13.2	—	2.8	—	14.7	10.2	12.1	4.5	2.6	+	+ sin. transv.
5	16.0	12.5	12.9	3.5	3.1	16.0	12.5	11.7	3.5	4.3	+	—
6	11.9?	8.9	9.6	5.2	4.5	15.8	9.2	—	6.6	—	+	—
7						15.2	10.8	—			—	—
8	15.3	10.7	—	4.6	—	16.0	10.8	10.2	5.2	5.8	+	—
9	17.5	8.9	10.7	8.6	6.8	17.5	13.0	12.2	4.5	5.3	+	— no satisfactory pictures
10	—	—	—	—	—	17.4	11.6	10.7	5.8	6.7	+	—
11	—	—	—	—	—	13.7	9.5	—	4.2	—	+	—
						—	10.0	8.1	6.0	8.5		
12	14.8	6.7	6.8	8.1	8.0	—	10.5	11.1	6.0	5.4	—	—
13	16.7	10.5	11.0	6.1	5.6	17.2	11.3	12.0	5.8	5.1	—	—
14	—	—	—	—	—	—	—	—	—	—	—	—

Δ_1 = (Carotis O_2 — Sinus sagitt. sup. O_2) vol.%.
Δ_2 = (Carotis O_2 — Contralateral jugul. int. O_2) vol.%.

This fact also explains why only the dilated jugular vein (see above) and not the internal carotid artery was filled at the follow-up angiography. The veins of the face and neck were also dilated and in one case progressive stasis of the optic discs was demonstrated. On account of this, re-operation on these patients was necessary; after the fistulae had been closed, the signs quickly regressed.

In one further case (11) where a narrow side-to-side fistula was made between the common carotid artery and the jugular vein, no such complications arose; nor did any complications arise in the remaining patients where end-to-side anastomoses between the external carotid artery and the internal jugular vein were performed.

In four cases (4, 6, 8 and 11) signs of moderate venous stasis taking the form of a reduced oxygen content in the superior sagittal sinus and signs of certain changes in the venous drainage were encountered. Direct sinography in all these cases showed strictly unilateral or marked predominant drainage from the superior sagittal sinus.

The short-circuited blood stream, according to the roentgen findings, in all probability follows the path of least resistance — it flows in the direction of the physiological fall in blood pressure towards the large venous drainage channels (vertebral plexus, condylar emissary vein and extensive collateral veins in the neck), which during the pre-operative roentgen investigations were not filled with contrast medium.

This confirms, inter alia, that without shutting off of large parts of the venous drainage channels from the skull no reversing of the circulation can be achieved. Not even in Case No. 4, with definite unilateral drainage from the superior sagittal sinus, could the contrast medium be forced higher up than into the transverse sinus after the carotid-jugular shunt.

These investigations show that with the operation in its present form arterial blood cannot be forced up via the jugular vein into the cortical veins. This is in accordance with the clinical results since practically no improvement was obtained.

A more extensive account of the operative technique and clinical results will be published in Acta Chirurgica Scandinavica.

SUMMARY

The possibility of supplying arterial blood to the brain (revascularisation) by means of an arteriovenous shunt was studied in 14 children with cerebral lesions.

Certain angiographic investigations were also carried out before and after the operation in order to determine any possible changes in the circulation. These were supplemented by oxygen analyses of the blood. It is shown that the dynamics of the cerebral circulation are affected by the anastomosis, but the conclusion is reached that the forcing of blood into the cortical veins is not achieved.

ZUSAMMENFASSUNG

Die Möglichkeit, dem Gehirn arterielles Blut durch einen arteriovenösen „Shunt" zuzuführen (Revaskularisation), wurde an 14 Kindern mit Gehirnschäden untersucht.

Gewisse angiographische Untersuchungen wurden vor und nach der Operation vorgenommen, um jede Veränderung der Blutzirkulation festzustellen; sie wurden durch Sauerstoffanalysen des Blutes vervollständigt. Es wird gezeigt, dass die Dynamik der zerebralen Zirkulation durch die Anastomose beeinflusst wird; jedoch wird der Schluss gezogen, dass ein Hineinpressen des Blutes in die kortikalen Venen nicht erreicht wird.

RÉSUMÉ

Les auteurs ont étudié la possibilité de revasculariser le cerveau grâce à un shunt artérioveineux chez 14 enfants atteints de lésions cérébrales.

Ils ont aussi pratiqué des examens angiographiques pré- et post-opératoires pour mettre en évidence les éventuelles modifications de la circulation et ont fait en outre des dosages d'oxygène dans le sang. Il est prouvé que la dynamique de la circulation cérébrale est modifiée par l'anastomose, mais on arrive à la conclusion que le sang ne pénètre pas dans les veines corticales.

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FROM THE ROENTGEN DEPARTMENT OF AKERSHUS COUNTY HOSPITAL AND OF AKER HOSPITAL, OSLO, NORWAY

ABDOMINAL AORTOGRAPHY

by

Torfinn Denstad

After the Portuguese authors Dos Santos, Lamas & Pereire Caldas had described the technique of abdominal aortography and cited their first 300 cases in 1929, and Osorio had reported 100 cases in 1932, several years elapsed before we again heard anything of the procedure. But from 1945 onwards a good deal has been written on the subject, especially in America, and it is evident that this important diagnostic method is steadily gaining ground. In Sweden 16 cases were published by Runström in 1947. In the same year Weyde reported 3 cases to the Norwegian Medical Society; some further interesting cases have also occasionally been demonstrated at the meetings. In December 1950 Weyde gave a survey of the method to the Oslo Surgical Society.

The material I myself have at my disposal is of comparatively modest extent and consists of 21 cases from Akershus County hospital and 76 from Aker Hospital, or 97 in all. I nevertheless consider it expedient to present this series at the present time as it would appear important that the experiences gained with this comparatively new diagnostic aid should be made known relatively early. Moreover, it may perhaps conduce to a more frequent adoption of the method which, without doubt, deserves to be much more widely employed.

I shall not go further into the technique; it has been fully described in various articles and handbooks. I shall merely mention that, with few exceptions, I have adopted local anesthesia; it has been found completely satisfactory and moreover, offers the advantage that the patients can be enjoined to hold their breath during the injection. The examination is thus rendered more simple and may be carried out single-handed — whereas certain American authors (Wagner et al.) demand a roentgenologist, two anesthetists and a surgeon. It must, however, be noted

Submitted for publication, Jan. 14, 1952.

that the Portuguese investigators and practically speaking all the Americans have used 10 ml of an 80 per cent sodium iodide solution as a contrast medium; this is so irritating and painful that it is necessary to employ narcosis — usually intravenously. We use 30 ml of 70 per cent Nycotrast (equivalent to Perabrodil), which generally gives an entirely satisfactory contrast. The injection is effected by hand.

The actual puncturing of the aorta is generally easily carried out. Several injections of physiologic salt solution during different phases of respiration will confirm that the point of the needle is properly in the lumen of the vessel. Even though permanent damage from extravasal injection has not been observed, its occurrence causes severe pain, which may last up to 24 hours, and everything possible must be done to avoid it.

Serious diffuse affections of the hepatic or renal parenchyma are contraindications to the procedure. Before making the injection one must, of course, make sure that the patient is not hypersensitive to iodine.

As regards complications, more than 3,000 examinations were reported in the literature up to 1948 without a death that could be ascribed to the injection procedure (MELICK & VITT). In 1950, however, WAGNER & PRICE reported a fatality which they considered was due to thrombosis of the superior mesenteric artery with gangrene of the intestine, nearly all the contrast medium having found its way into that vessel. They used an 80 per cent sodium iodide solution. We too have not infrequently found that the contrast selectively fills one main branch of the aorta, for instance, one of the renal arteries or the superior mesenteric artery, without however, any damage being caused. The organic iodine compound in the Perabrodil preparations is certainly considerably less irritating and toxic than the inorganic sodium iodide salt, and ought therefore to be exclusively employed. Transient iodism is, as we know, not infrequently seen after use of sodium iodide. NELSON has, however, not been able to detect any changes in the intima of the renal arteries on examination of extirpated kidneys after aortography with a solution of 80 per cent sodium iodide.

We have not had any complications.

An exact appreciation of the anatomy of the abdominal organs and especially of their arterial supply is a necessary requirement for gaining the greatest possible profit from the aortographic examination (Fig. 1). The course and appearance of the finer renal arteries vanishing towards the periphery, and resembling the thin strokes of a brush, must especially be noted. By puncturing the aorta at various levels one can, to some extent, determine which branch will become best filled with the contrast, although for the most part this will be dependent on fortuitous

Fig. 1. Normal aortogram. Good contrast filling of the inferior phrenic artery and the following branches of the coeliac artery: the splenic, left gastric, hepatic (with its right and left branches and cystic) and gastro-duodenal (with the gastro-epiploic and pancreatico-duodenal). Renal arteries also outlined. The superior and inferior mesenteric arteries less well filled.

circumstances. In order that the contrast may fill the vessels in a particular area it may be necessary to make several punctures.

What profit may we hope to gain from the investigation? What pathologic changes may we except to see?

They may be roughly classified as follows:

1) *Lesions of arteries*, including anomalies and atrophy or hypertrophy (secondary to altered functioning of the organ concerned).

To these belong aberrant renal arteries (5 cases), the detection of which is of importance in cases where they impede the emptying of the renal pelves.

I have recently performed (ambulatorily) aortography on a young man, in whom hydronephrosis had been diagnosed. The examination confirmed the suspicion that an aberrant vessel was the cause. The vessel was subsequently resected, together with the portion of the lower renal pole which it supplied.

Arteriosclerosis, aneurysms (2 cases) and thrombosis (2 cases) will be detected by the method, and this may be a matter of considerable importance (Figs. 2 & 3). LERICHE has drawn attention to the often in-

Fig. 2. Aneurysm of the abdominal aorta. Fusiform enlargement of the calcified aortic wall, with thrombosed or organised deposits on the inner side. Arcuate displacements of the mesenteric vessels.

Fig. 3. Thrombosis of the abdominal aorta. Aortography shows complete occlusion at the level of the third lumbar vertebra.

sidious development of thrombosis of the aorta and the iliac arteries, and has described the typical signs. He believes the disease to be considerably more common than is generally supposed.

Renal dysplasia (for instance, an ectopic kidney), or agenesia will also be revealed by an atypical course or absence of the renal artery (5 cases).

Aortographic studies of *the atrophy and hypertrophy of the arteries* must be expected in many cases to give us valuable information respecting the function of the organ concerned. The blood supply to the kid-

Fig. 4. Aortography in a case of right-sided hydronephrosis with stone:
Hypoplasia of right renal artery, the branches of which are extended.

neys is of particular interest, and here we have the advantage of being able to compare the two sides. We must however, be very cautious in our judgment. For instance, if the contrast medium be injected chiefly into one renal artery, we may easily obtain a false impression of the difference in calibre of the vessels. In case of chronic unilateral affections with destruction of the parenchyma of the kidney (hydronephrosis, pyelonephritis), we shall however, in many cases receive a convincing impression of the difference in the blood supply with reduced flow to the diseased and increased flow to the healthy organ. Doss lays great weight on these signs when it is a question of indication for operation and choice of operative method in cases of impediment at the site of transition from renal pelvis to ureter — often occasioned by an aberrant vessel. In such cases aortography may yield valuable information on three matters: 1) Proof or otherwise of the presence of an aberrant vessel, 2) as to the blood supply of the kidney and thereby of its function and 3) as to how large a part of the kidney is supplied by the aberrant vessel and would have to be resected if the function were deemed to be so good that nephrectomy could be avoided.

Important information may also be obtained by means of aortography in cases of hypertension, even though the 'Goldblatt kidney' does not play so important a rôle in the genesis of hypertension as was at first believed and, we may well say, hoped. WAGNER, PRICE &

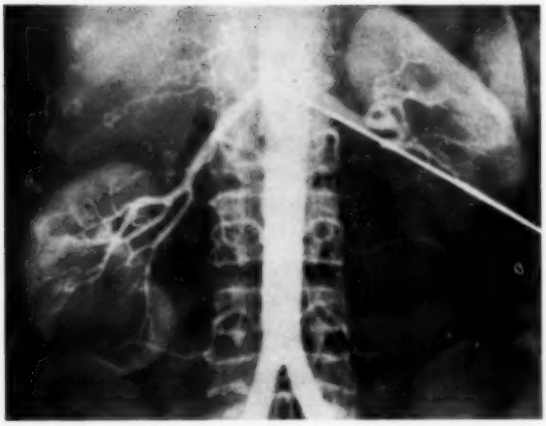

Fig. 5. Solitary renal cyst on right side. The arteries are forced apart in the lower pole of the kidney where there is a plum-sized defect in the otherwise 'contrast-filled' right kidney (nephrogram). The diagnosis of cyst was verified by puncture and the injection of contrast.

SWANSON recommend aortography before the eventual performance of sympathectomy and Doss categorically states: "No patient, having an unexplained hypertension, has been completely investigated without the inclusion of translumbar arteriography . . .".

2) Another important group in the field of indications is composed of diseases which lead to *displacement of the arteries in a particular organ.* Here again it is the kidneys that claim attention. Hydronephrosis or pyonephrosis (2 cases) may be revealed by aortography in cases in which the function is so much impaired that urography fails and retrograde pyelography cannot perhaps be employed (Fig. 4). At the same time, an idea of the blood supply is obtained, as mentioned above. Doss warns against retrograde pyelography in such cases in view of the danger of infection unless the catheter be allowed to remain in the ureter or operation carried out immediately.

Expansive processes in the kidneys may force the vessels apart and appear as poorly vascularized areas. This applies especially to renal cysts (15 cases) (Fig. 5). Such cysts may be still more distinctly revealed on a roentgenogram taken some few seconds after the injection (a nephrogram); the contrast fluid chiefly fills the capillaries and the cysts, if sufficiently large, appear as well-defined non-opaque areas. They may, however, be difficult to detect, either because the survey is hindered by mesenteric vessels filled with contrast fluid, or because they are too small. On the whole, it is my impression that cysts are better depicted by deformation of the urogram or retrograde pyloegram than by the aortogram. However, an aortographic examination is of value in these cases on account of the information it furnishes for differential diagnosis.

Fig. 6. Hugh solitary cyst on left side. Arcuate displacement upwards of the splenic artery and downwards of the renal artery. One artery (probably the left colic) is extended over the tumour. Puncture revealed a cyst.

Large tumours may displace not only the renal arteries and their branches, but the other intra-abdominal arteries. In such cases it may be difficult to decide whether the tumour (cyst) originates from the kidney, the adrenal gland or perhaps the pancreas (Fig. 6).

3) We now come to an important group in which successful aortography at once gives the diagnosis, which may otherwise be difficult to establish. This group embraces *malignant tumours*, richly vascularized with numerous newly-formed pathologic vessels. BILLING and LINDGREN have appealed for a closer study and survey of the angio-architecture of malignant tumours, and have reported the finding of numerous pathologic vessels in hypernephromata, whereas they have hardly ever been able to detect such vessels in carcinomata of the stomach. I have previously reported two cases in which metastases from a malignant melanoma and a malignant neurinoma were revealed on arteriographic examination — in one of the cases by aortography. This summer we have had a similar case at the Aker hospital (Fig. 7).

Otherwise it is the diagnosis of renal diseases that is of special interest in this group, seeing that, as mentioned above, the carcinomata

Fig. 7. Malignant abdominal tumour. Soft-tissue shadow the size of a coconut upwards to the right, merging into the shadow of the liver. Numerous tumour-vessels of irregular form and unequal calibre, possibly from the suprarenal artery. The hepatic artery and its branches seem to be displaced in a medial direction and the upper part of the abdominal aorta towards the left. Regarded as inoperable (hematothorax present). Biopsy: Neurinoma.

(hypernephromata) (10 cases) are distinguished by a characteristic picture with numerous blood-vessels of irregular calibre and course and slow circulation with retention of contrast fluid (Fig. 8). Several such cases are reported in the literature. Thus NELSON has described two cases with normal urograms and in which the diagnosis was established by aortography, in one case bilateral.

WAGNER has described a case of liposarcoma with pathologic vessels and retention of the contrast medium, so that such findings should not warrant more than a general diagnosis of malignant tumour.

Failure to discover a pathologic network of vessels, however, does not preclude the presence of a malignant growth. I have myself had a case with an *adenocarcinoma* about the size of an orange and in which the vessels at the site of the tumour were but scantily filled (Fig. 9). This also accords with the experiences of other investigators (DOSS, MELICK & VITT, SANTE). One can rely only on positive findings.

Fig. 8.

Fig. 9.

Fig. 8. Renal carcinoma (hypernephroma). Hypertrophy of right renal artery, especially of the lower branches over an area where the contrast medium is retained in numerous irregular formed vessels. No distinct filling of vessels in the enlarged lower pole of the kidney (probably due to necrosis). Nephrectomy: Mandarin-sized tumour in lower renal pole.

Fig. 9. Adenocarcinoma of the kidney. No obvious contrast-filled vessels in lower part of right kidney where at operation an orange-sized tumour was found.

4) The last group comprises expansive processes which manifest themselves only by *displacement of the large arteries*. To it belong, first of all, the retroperitoneal and mesenteric tumours (8 cases), although, of course, every growth of any considerable size in the abdomen may

a. b.

Fig. 10 a—b. Retroperitoneal lymphosarcoma. Aortography (two planes): The tumour displaces the abdominal artery in an arch to the right and extends the mesenteric vessels. Explorative laparotomy: Inoperable nodular tumour the size of a human skull at the root of the mesentery.

cause such changes. We here have a difficult field of diagnosis, as such tumours are slow in causing symptoms and present few signs. In many cases they come for treatment so late that every form of therapy is fruitless. We had therefore hoped to have found in aortography a means of detecting these tumours at an early stage. We have, however, been sadly disappointed, as the growths are as a rule not so well vascularized that pathologic vessels can be discerned with certainty. In most cases, the tumours will be sarcomata arising from the retroperitoneal fat and connective tissue or from lymphoid tissue at the base of the mesentery (Fig. 10). We have also had seven other cases with large retroperitoneal masses in which we were unable to discover pathologic vessels. NELSON has described a multilocular peritoneal tumour and WAGNER et al. a retroperitoneal sarcoma, both without pathologic vessels. Doss states that "the arterial supply to such structure is difficult to visualize". Lymphogranulomatosis and pancreatic tumours also seem to come under this category.

We must therefore admit that only particular types of retroperitoneal tumours can be diagnosed at an early stage by means of aortography (cf. the preceding group).

There still remain several fields in which aortography may be supposed to furnish valuable information, but on which I have not touched by reason of lack of experience. I may mention nephrosclerosis (in which the renal function is not so reduced that an aortographic examination is contraindicated), chronic hepatitis and cirrhosis, thrombosis of the splenic artery and vein, as well as of the mesenteric vessels, or emboli therein, strangulated ileus with obstructed circulation, and carcinomatous metastases in the liver and peritoneum (cf. arteriographic detection of metastases in the brain). In one case the aortography demonstrated several pathologic hepatic vessels. The occurrence of carcinomatous metastases was verified by the postmortem examination. Aortography has also been employed to reveal placenta previa (HARTNETT). We have performed aortography in five cases of renal tuberculosis, both incipient and far-advanced, without being able to note any definite changes. Information however, as to the blood supply will, of course, be of importance in regard to the extent of resection indicated.

First and foremost, however, it is important to obtain a chart of the blood supply of malignant tumours and then to bear in minds which tumours may be considered in association with a network of pathologic vessels and which tumours cannot be expected to reveal such vessels. Account must be taken of the fact that the same form of growth may present a different angiographic picture if necrosis be present.

SUMMARY

The author reviews the procedure of abdominal aortography with special reference to its value in renal investigations based upon a material of 97 cases. It is particularly pointed out that atrophy or hypertrophy of the renal arteries is indicative of reduced or increased function respectively; the examination is of special importance for the detection of cysts of the kidneys and hydronephroses in cases of greatly impaired renal function. Conclusions regarding pathologic vessels in malignant tumours may only be drawn from positive findings. The increasing importance and value of abdominal aortography is stressed.

ZUSAMMENFASSUNG

Der Verf. gibt einen Überblick über die Ausführung der abdominalen Aortographie mit besonderer Rücksichtnahme auf ihren Wert bei Nierenuntersuchung; er stützt sich auf ein Material von 97 Fällen. Es wird besonders hervorgehoben, dass die Atrophie oder die Hypertrophie der Nierenarterien eine herabgesetzte bezw. erhöhte Funktion aufweist. Die Untersuchung ist von besonderer Bedeutung für die Entdeckung von Nierenzysten und von Hydronephrosen in Fällen mit stark herabgesetzter Nierenfunktion. Schlussfolgerungen bezüglich pathologischer Gefässe in bösartigen Geschwülsten sollten nur aus positiven Befunden gezogen werden. Die zunehmende Bedeutung und der Wert der abdominalen Aortographie wird hervorgehoben.

RÉSUMÉ

L'auteur rappelle la technique de l'aortographie abdominale et, se basant sur un matériel de 97 cas, étudie spécialement sa valeur dans les examens rénaux. Il insiste particulièrement sur le fait que l'atrophie ou l'hypertrophie des artères rénales indiquent respectivement une diminution ou une augmentation du fonctionnement rénal; cet examen est particulièrement utile dans la recherche de kystes rénaux et d'hydronéphroses dans les cas où la fonction rénale est très atteinte. On ne peut conclure à l'existence de vaisseaux pathologiques dans des tumeurs malignes que sur des résultats positifs. L'auteur souligne l'importance croissante et la valeur de l'aortographie abdominale.

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FROM THE ROENTGEN DIAGNOSTIC DEPARTMENT, MUNICIPAL HOSPITAL OF AARHUS AND THE RADIUM CENTRE FOR JUTLAND, AARHUS, DENMARK (DIRECTOR: PROF. CARL KREBS)

TOMOGRAPHY OF THE GALL-BLADDER

by

Poul E. Andersen

Every radiologist is acquainted with the difficulties encountered in the diagnosis of non-opaque gall-stones by means of cholecystography. The patient is usually obese and the emptying of the bowel may be incomplete, with feces and gases obscuring the gall-bladder region; the outline of the pathologic gall-bladder may often be faint, even after a double dose of the contrast medium, or may be obscured by the ribs and costal cartilages. All these result in difficulties in evaluating the roentgenograms. The author wishes to draw attention to the often very considerable aid which tomography may render in such cases.

The technique is a simple one. The patient is prepared as usual, and cholecystography (peroral method) is carried out in the ordinary manner. From the roentgenograms of the gall-bladder region in the prone position, the location of the gall-bladder is determined. After careful centring, tomograms are obtained, usually at 3 to 8 cm from the plane of the top of the table, depending on the thickness of the patient, supplemented if necessary by additional sections at 0.5 cm intervals. Tomography may be repeated after the fatty meal has been given, if no definite diagnosis has been made.

During the last year this method has been used at the Roentgen Diagnostic Department of the Municipal Hospital, Aarhus, with excellent results. In several cases it has been possible to disperse overlying or underlying opacities and leave a faint gall-bladder shadow relatively unobscured, thus demonstrating stones and other anomalies which could not be revealed by the usual methods.

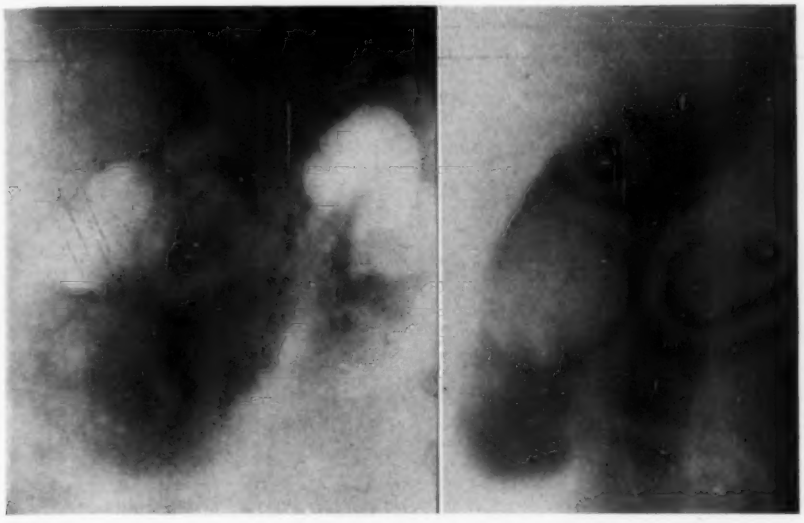
A few examples will show the advantages of tomography in difficult cases.

Submitted for publication, Febr. 12, 1952.

Fig. 1. Case 1. Gall-bladder obscured by a rib and calcifications in the costal cartilages (above). Tomograms taken at different levels showing one large and several small concrements (below).

Case 1. A woman, aged 28, very obese, with symptoms of cholelithiasis for 9 years. Cholecystography: on the film taken in the prone position, a rather faint gall-bladder shadow was seen almost completely obscured by a rib and the costal cartilages (Fig. 1 a). The gall-bladder — containing at least one large stone — could not be projected free in the prone, oblique or lateral positions. Tomography revealed a faint gall-bladder shadow containing one large stone, the size of a walnut, with a denser layer a few millimeters below its surface, and several small facetted stones at the fundus (Figs. 1 b and 1 c).

Cholecystectomy was performed in the Surgical Department of the University Hospital. The removed gall-bladder was completely filled by one large and several small, pea-sized, facetted stones. The tomographic findings were thus verified by the operative findings.



a. b.

Fig. 2. Case 2. a) Probably a stone in the partially concealed gall-bladder. b) Tomogram confirmed the diagnosis.

Case 2. A woman, aged 44, with a 24-years history of gall-bladder disease.

Cholecystography showed a large, rather faint gall-bladder shadow, partially concealed by gases and feces in the ascending and transverse colon. The presence of at least one large stone was suspected. This was confirmed by tomography. (Figs. 2 a and 2 b.) On account of previous unfortunate experiences in her family, the patient, in spite of severe symptoms, refused operation.

Case 3. A woman, aged 56, obese, with adenocarcinoma of the corpus uteri, diabetes mellitus, hypertension, rheumatic heart disease and severe bronchitis. She had for several years had clinical signs of cholelithiasis. Cholecystography revealed a gall-bladder with a diverticulum, partially concealed by gas in the region of the hepatic flexure of the colon. Filling defects could be observed both at the fundus and in the diverticulum, but could not be projected free from the bowel gases (Fig. 3 a). Tomography was carried out. The 3.5 cm layer (Fig. 3 b) showed several small facetted calculi and at 5 cm (Fig. 3 c), one larger stone with a central calcium core with radiating beams was seen lying at the fundus of the gall-bladder. The patient being a very poor risk, cholecystectomy was not performed.

In several cases, tomography has shown the gall-bladder to be clear by dispersing shadows cast by calcifications of the costal cartilages or by gas. Figs. 4 a and 4 b are from such a case with a normal gall-bladder. Surgical verification was of course, not possible. In almost all these

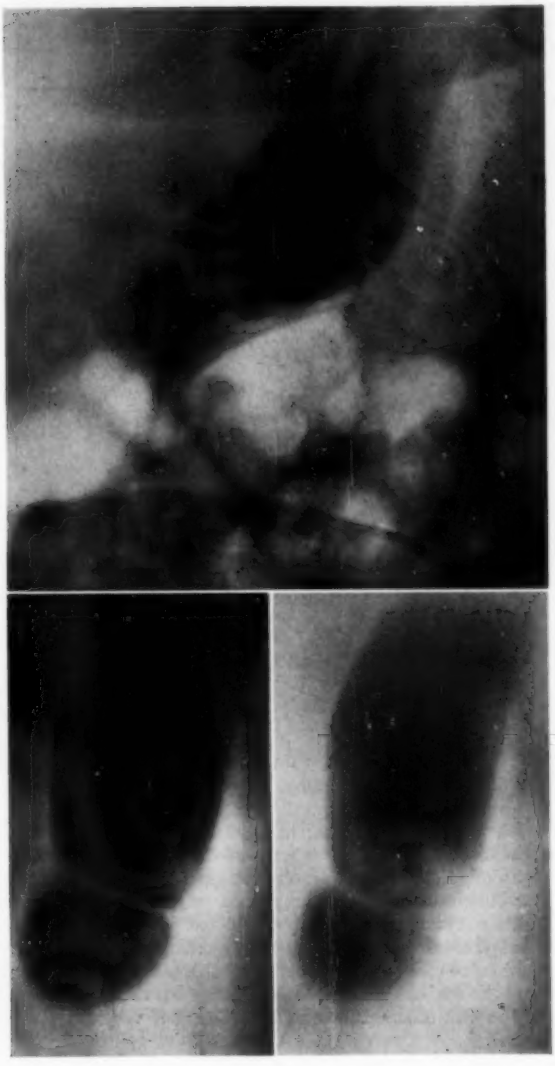


Fig. 3. Case 3. Above: Conventional roentgenogram. Below: Tomograms. Several concrements.

cases a definite diagnosis explaining the patient's symptoms was reached and as it has been found possible to demonstrate stones of the size of a pin's head, it is hardly likely that any would have been missed when tomography was carried out with close intervals between the layers.

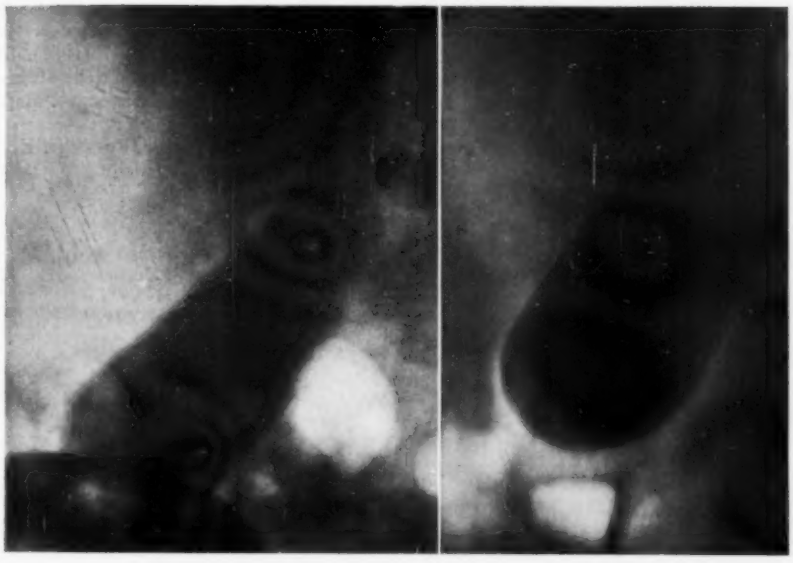


Fig. 4. Left: Conventional roentgenogram. Right: Tomogram. No concrements.

SUMMARY

The author recommends the use of tomography in cholecystography in certain cases after the free projection of the gall-bladder has proved difficult (for instance in cases with insufficient emptying of the bowel).

ZUSAMMENFASSUNG

Der Verfasser schlägt vor, die Cholecystographie in den Fällen mit einer Tomographie zu komplettieren, wo es sich als schwierig erweist, die Gallenblase freizuprojizieren (z. B. in Fällen mit unvollständiger Entleerung des Darmes).

RÉSUMÉ

L'auteur préconise l'emploi de la tomographie au cours de la cholécystographie dans certains cas où la projection séparée de la vésicule biliaire s'est avérée délicate (par exemple dans les cas où l'intestin se vide insuffisamment).

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TOMOGRAPHIC ANALYSIS OF ARTERIOVENOUS ANEURYSMS IN THE LUNG

Report of a case confirmed at autopsy

by

Herman Lodin

Arteriovenous aneurysms in the lungs have attracted increasing attention in recent years, due to advances in thoracic surgery having made them more amenable to treatment. A properly planned operation for aneurysms requires as complete a knowledge as possible of their number, sites and vascular relations. An ordinary roentgen examination will not usually meet all these requirements, although, as pointed out by LINDGREN (1946), possibly adequate for diagnostic purposes. Preoperatively the routine roentgen examination must in general be supplemented with tomography or angiography. The latter procedure is best for detailed studies of the vessels. But tomography also makes for a more refined diagnosis: not only do aneurysms that are visible on routine films become much clearer but others that otherwise would have gone unnoticed, may even be disclosed. A report of a case follows in which tomography had surprising results.

The patient (M. 3043/1951) was a 26 years old student who since childhood had been cyanotic after exertion. He had typical clubbed fingers and a drawn-out systolic murmur was heard over the second intercostal space on the right side. The latter had been interpreted as a sign of congenital heart failure, but occasional roentgen examinations had revealed nothing untoward and the configuration and volume of the heart were normal. Towards the end of December 1951 he was admitted to the medical ward of the University Hospital, Upsala, for contraction of the visual fields and nuchal headache. A young man of slender build, the patient had neither cyanosis nor dyspnea and no teleangiectasis. He had typical clubbed fingers and spoon nails. *The Heart:* Voussure and frémissement were noted and in the second intercostal space on the right side a

Submitted for publication, April 17, 1952.

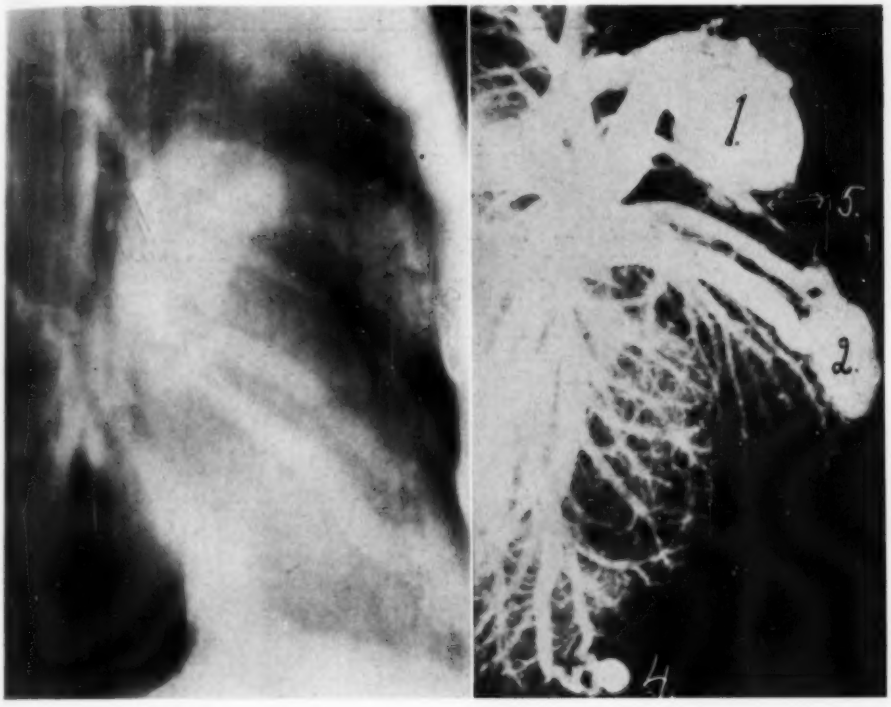
a. b.

Figs 1 a and b. A.p. and lateral views. The A.p. view (1 a) shows a density in the right hilar region and another along the right border of the heart. These correspond on the lateral view (1 b) to tumour-like opacities in the ventral part of the superior lobe and in the intermediate lobe; they are connected to the hilus by ribbon-like densities — arteriovenous aneurysms.

drawn-out systolic murmur was heard: the rhythm was even and the rate normal; a capillary pulse was present; the blood pressure was 140/90; the ECG: normal. *The lungs* displayed nothing abnormal. *Blood:* Hb 122 per cent; RBC. 5.6 millions. After a time meningitis and abscess in the left posterior lobe of the brain developed. The abscess broke through to the ventricular system and led to the patient's death. At the post-mortem examination which followed, the heart and lungs were excised and the vessels of the lungs filled with a contrast medium injected into the pulmonary artery.

Roentgen findings: No signs of heart failure were seen in the posterior-anterior, lateral (Figs. 1 a and b) or oblique views on ordinary roentgen examination. The configuration and volume — 310 ml/sq.m. of body surface — were normal. In the a. p. film (Fig. 1 a), however, there was a density in the right hilar region as well as a more elongated opacity along the right border of the heart. These findings were explained in the lateral view (Fig. 1 b). In the ventral medial part of the superior lobe a lobulous, tumour-like density rather bigger than a plum and in the ventral caudal part of the middle lobe a similar but smaller density, were observed. Both these opacities were connected with the hilus by ribbon-like shadows. Such findings are typical of arterio-venous aneurysms. Situated near the medial line and the ascending aorta, the large aneurysm with its drawn-out murmur had misled the clinicians into diagnosing congenital heart failure. These two aneurysms apart, the routine examination disclosed nothing abnormal. However, a later tomographic analysis of the lungs produced the following results.

The *lateral tomogram* (Fig. 2 a) shows more clearly than the routine films the two large aneurysms with their afferent and efferent vessels. Yet another vessel is seen bulging



a. b.

Figs. 2 a and b. Lateral tomograms and the corresponding pathologico-anatomic specimen. In the lateral tomogram (2 a) the arteriovenous aneurysms stand out much more clearly. Between them a vessel which widens into a club-shaped bulge — another aneurysm. In the necropsy specimen (2 b) these aneurysms are filled with contrast (Nos. 1, 2 and 5). Further aneurysm in basal region of the lower lobe (No. 4).

like a club between these two aneurysms close to the ventral aspect of the lung and represents a further arteriovenous anastomosis. All these findings are confirmed in the film of the pathologico-anatomic specimen (Fig. 2 b). In the dorsal part of the inferior lobe, a vessel which does not narrow normally towards the periphery but retains its calibre unchanged, is seen (Fig. 3). It constitutes one arm of an arteriovenous shunt which may be seen in the extreme basal part of the necropsy specimen (Fig. 2 b). These two small aneurysms that are visible on the tomograms would obviously be indistinguishable in the ordinary roentgen film of the lungs. What is rather remarkable however, is that the large arteriovenous aneurysm seen on the lateral tomogram (Fig. 4) and situated in the superior part of the inferior lobe close to the interlobar fissure is not apparent on the routine roentgenograms. The tomogram very distinctly reveals both the aneurysm itself and the afferent artery superiorly and the efferent vein inferiorly. As is seen in Fig. 5 the latter aneurysm had a marked shunting action. The contrast medium returned

Fig. 3. Lateral tomogram. A vessel of uniform calibre is seen in the postero-basal part of the lower lobe with the associated aneurysm filled with contrast (Fig. 2 b, No. 4).

Fig. 4. Lateral tomogram. The upper part of the lower lobe contains an arteriovenous aneurysm with the artery running upwards and the veins downwards.

via the aneurysm directly to the heart through the pulmonary veins without filling the small peripheral vessels elsewhere in the lung. In order to outline the remaining parts of the circulatory system of the lung, it was necessary to tie off the pulmonary veins.

The *a.p. tomogram* (Fig. 6) displays a vessel running to the apex of the lung without narrowing normally. Medially to it, another vessel with the same abnormality, is seen. These two vessels join and form an arteriovenous anastomosis that is better studied in the film showing the post-mortem appearances (Fig. 7) and in which the gradual filling of the anastomosis with the contrast medium may be observed. One sees how the artery merges with the vein practically without forming an aneurysm. This probably represents an early state of a large aneurysm. Being invisible on ordinary roentgenograms, such small aneurysms cannot be diagnosed without the use of tomography or angiography. A tomographic examination of the left lung disclosed no vascular malformations and an angiographic examination produced a similar result.

Discussion. The routine roentgen examination showed that the condition was not one of congenital heart failure but of arteriovenous aneurysms in the right lung. These were causing the patient's cyanosis, clubbed fingers and murmur. Despite the large arteriovenous aneurysms, the heart volume was normal — a confirmation of previous reports.

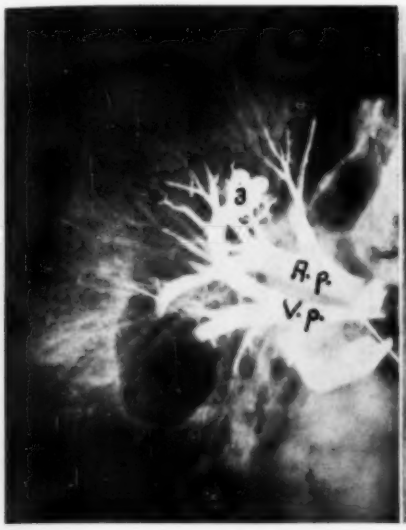


Fig. 5. Necropsy specimen. Contrast has passed from the pulmonary artery (A. P.) through the aneurysm (No. 3) to the pulmonary vein (V. P.)

Fig. 6. A.p. tomogram. A small vessel of uniform calibre runs towards the apex. Medially to it, another vessel of the same appearance.

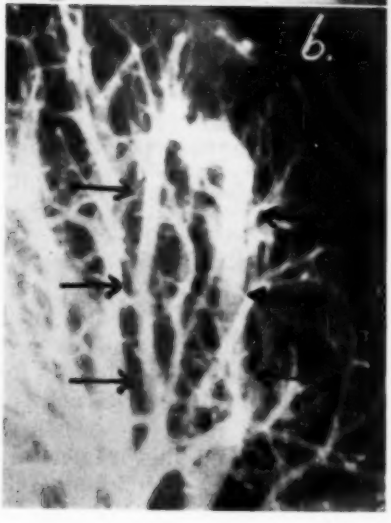
The two large aneurysms also appear in films from earlier roentgen examinations. However, a tomographic examination disclosed four additional aneurysms, one of which was of considerable magnitude. The vessels to the latter were remarkably large compared with the size of the aneurysm itself. That may be why in the ordinary roentgen film this arteriovenous aneurysm is masked by the normal structure of the lung, especially as the region of the hilus is very complex and therefore difficult to analyze in detail. As a matter of fact, the aneurysm itself generally predominates in the form of a lobulous opacity resembling a tumour, and only on close inspection do the afferent and efferent vessels that are so important for a differential diagnosis appear.

It follows that the tomographic examination should include a close inspection of all the vessels in the region where no abnormal opacities are to be found in the general views. *A vessel proceeding towards the periphery without narrowing normally is pathognomonic of an arteriovenous shunt.*

In the case described, the tomographic and post-mortem angiographic findings fully agreed. Tomography is accordingly a valuable aid in the detailed analysis of the vascular anatomy of the lungs.

a.

b.



c.

Fig. 7. Necropsy specimen.
Aneurysm No. 6 filled with contrast
(artery →, vein ←).

SUMMARY

The case is reported of a patient with arteriovenous aneurysms which were analyzed by tomography. Angiography at post-mortem fully confirmed the tomographic findings.

ZUSAMMENFASSUNG

Bericht über einen Patienten mit arteriovenösen Aneurysmen; diese wurden durch eine Tomographie analysiert. Die post mortem ausgeführte Angiographie bestätigte die tomographischen Befunde.

RÉSUMÉ

Présentation du cas d'un malade atteint d'anévrysmes artérioveneux du poumon étudiés par tomographie. L'angiographie post-mortem a pleinement confirmé les résultats des examens tomographiques.

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A COMPRESSION APPARATUS FOR UROGRAPHY

by

Ragnar Steinert

One of the objects in urography is to demonstrate the morphology of the urinary tract. In order to obtain adequate distension of the pelves and calices by the contrast medium, ureteral compression must necessarily be used. This is often achieved by means of a cushion or pad placed on the abdomen at the approximate level of the sacral promontory and pressed down by a band attached to the table on which the patient is lying — a procedure which is generally most uncomfortable. By some workers two smaller pads — one for each ureter — instead of one are used and pressure on the great vessels and nerves lying in the mid-line of the abdomen is thus avoided. The main drawback of these methods is the impossibility of turning the patient if oblique projections are required. Great improvement is attained if the compression device be attached to the patient instead of the table. In the Scandinavian countries the compression device of LUNDSTRÖM (described in 1937) is widely used. This device consists of a rubber balloon, which is laid under a perspex sheet, in turn secured to the patient's abdomen by a band placed around the waist. By inflating the balloon, pressure on the ureters is obtained.

The author has combined the advantages of a device secured to the patient and of pressure exerted on each individual ureter in an apparatus which has been constructed with the assistance of an equipment engineer.

In place of one large rubber balloon, two smaller balloons situated one on each side of the mid-line below the umbilicus are used. With the aid of valves mounted on rubber tubes leading to each balloon it is possible to pump up both simultaneously or each one separately with varying pressure, as desired. This is an advantage should it be deemed necessary to compress one ureter more than the other — or conversely, to diminish

Paper read at the 17th Congress of The Northern Association for Radiology, Aarhus, Denmark, June 1951; submitted for publication Dec. 15, 1951.

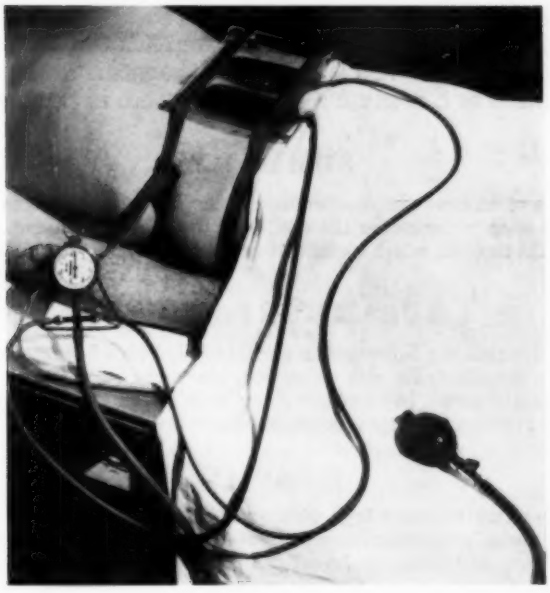

Fig. 1.

the pressure — during the examination. The tubes are connected with an ordinary manometer in such a manner that the pressure in each balloon may be measured separately. If the patient has only one kidney it is of course only necessary to inflate one balloon. The balloons are secured to the abdomen by a sheet of plastic material; a smaller sheet for infants is supplied with each apparatus. The belt which is placed around the patient to hold the balloons and plastic sheet in position, is fitted with strong leather straps. The manometer and the valves are bolted firmly on to a further plastic sheet to which is attached a heavy metal back support, the whole standing firmly in an upright slanting position and ensuring easy manipulation of the valves and manometer. If desired the control panel may be placed on a table by the patients' side. The apparatus may be used without the standard manometer; the tube line running to it is then replaced by the tube of a common blood-pressure apparatus, the arm-band of which has been removed. A Riva Rocci blood-pressure apparatus is usually available in most departments.

Up to the present we have used the apparatus for a fairly large number of examinations and have been satisfied with the results. It has been our impression, for example, that patients tolerate higher pressures on the

abdomen and have less subjective discomfort when this method of compression is used; a more direct pressure on each separate ureter rather than a diffuse pressure over a large area of the median region of the lower abdomen appears to constitute a distinct advance in pressure urography.

SUMMARY

A new type of ureteral compression apparatus which enables pressure to be exerted separately upon each ureter rather than diffusely over the lower abdomen, is described. Advantages of the method, which include its better tolerance by the patient, are pointed out.

ZUSAMMENFASSUNG

Ein neuer Apparat zur Kompression der Harnleiter wird beschrieben; er erlaubt es, Druck auf jeden Harnleiter für sich auszuüben, also nicht nur diffusen Druck über den unteren Teil des Abdomens. Die Vorteile dieser Methode, in welche die bessere Verträglichkeit für den Patienten einbegriffen ist, werden aufgezeigt.

RÉSUMÉ

Description d'un nouveau type d'appareil de compression urétérale qui perme d'exercer la compression sur chaque urétère séparément, et non d'une façon diffuse su la partie inférieure de l'abdomen. Avantages de la méthode, entre autres sa meilleure tolérance par le malade.

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AUTOMATIC COUNTING OF RADIOGRAPHS: AN AID IN PROCESSING CONTROL

by

Ove Mattsson

Information about the quantity of radiographic film processed, *e. g.* in a day, in a radiographic clinic may be of considerable value. It is of importance, inter alia, for judging the need of renewing developing and fixing baths or wetting agents, for statistical analysis of the capacity of the clinic and for planning film ordering.

The *number* of films of course gives no indication of the exact total *film surface*. This surface depends on the percentage of the different sizes, which in turn varies with the character of the radiographic work performed. The examination routine, however, is fairly constant in most radiographic departments, and the proportion between the different examinations does not fluctuate very much even if obvious variations occur from day to day. An approximate relationship between film surface and film number may be gauged for every radiographic department. It fluctuates to some extent with the seasons of the year — in winter and spring there are more examination of lungs, paranasal sinuses and mastoids, for example. Although the counting of films does not give any great degree of precision if information regarding the total quantity of film processed during a certain period be desired, the statistical results produced are acceptable for the majority of purposes, especially if the values obtained are judged critically.

To count the films manually, *e. g.* during sorting after drying, is time-consuming, particularly as the films are processed at different periods; some, while still wet may have been lent to surgical departments, 'throw-outs' already discarded, etc.

The simplest method is to make the counting automatic in connection

Submitted for publication, February 29, 1952.

with the *marking* of the patient's name etc. on the films. In Sweden this marking is normally done with a device designed by ÅKERLUND (1931) and recently slightly modified. Each film is marked only *once*, and *all* films are marked with the patients' names.

The principle of Åkerlund's marking apparatus is well known.

(The marking apparatus of Åkerlund's type is manufactured by G. Schönander AB, Stockholm. A new model will be equipped with counting arrangement and also have a timer for correct illumination in marking.)

It produces a photographic recording of the patient's name and year of birth, the date on which the radiograph was made, as well as the name of the hospital. The film is pressed against a narrow slit in which the text and figures are placed, on paper and celluloid, respectively. By switching on a lamp for a short period these entries are transferred to the film by a kind of photographic printing; the switching is effected automatically when a lever which also holds the film in position during the exposure is depressed. The lamp may also be lighted independently to check the name, etc.

By making the downward movement of the positioning lever act on a switch and close a circuit activating an *electric counter* of the type used by telephone companies for registering telephone calls, an exact count can be made of the number of marking operations, and hence of the number of films.

Fig. 1. A detail of a marking apparatus of Åkerlund's design with arrangement for counting. The downward movement of the lever which holds the film in position for marking is made to act on a small pin (indicated by an arrow) which acts on a micro-switch inside the apparatus.

Fig. 2. The layout of the arrangement with the small pin activating the switch which gives an impulse to the counter.

The technical layout of the apparatus is simple. The lever arrangement which holds the film in position for marking acts on a pin which activates a micro-switch, as shown in Figs. 1 and 2. When the circuit is closed, the counter receives an impulse and a new figure is registered electromagnetically. Each impulse turns a figure wheel a short distance past a ratchet. The dial usually has five figures, which means that it registers from 0 to 99,999 and then starts again from zero. The current used may be of low voltage: counters for 8 to 10 volts are normal electrotechnical instruments, such as those used for telephone communication. In such cases the power may be supplied via a transformer and rectifier or from a battery. There are also counters for 110 or 220 volts a. c. so that direct application of the same voltage as that of the marking circuits is possible. If more than one marking unit be used in the same darkroom, they may all be connected to the same counter, and in which case the impulses are added automatically. The counter may be mounted inside or outside the darkroom. Fig. 3 shows a counter mounted in the daylight close to the light-trap to the darkroom and thus easy to read. It serves two marking apparatus. It is good practice to note the total figure on the counter at the end of every day's work: the additional number of films marked is obtained by simple subtraction. For small radiographic departments where only one marking apparatus is needed, it is also possible to use a mechanical counter incorporated in the box of the marking unit.

Fig. 3. A counter mounted in the daylight close to the light-trap to the dark room. It serves two marking apparatus. In this case the counter is mounted in a wooden box. A signal lamp and press buttons for current and counting control.

The principle of the automatic counting of radiographs may also readily be adapted to the marking arrangements described by KJELLBERG (1939) and WOOD (1949).

By determining fairly exactly in this way the quantities of film passing through the developer, a more objective estimation of developing time and of regeneration and renewal of the solution is possible, with a subsequent greater constancy in the results attained.

SUMMARY

The author describes a simple modification to the standard film-marking device enabling the counting of radiographs to be carried out automatically. It is claimed that its use affords better control as regards the renewing of processing agents. It facilitates statistics of the work done in the department.

ZUSAMMENFASSUNG

Der Verfasser beschreibt eine einfache Modifikation des gewöhnlichen Markierungsapparates für Filme die ein automatisches Zählen der hergestellten Röntgenaufnahmen ermöglicht. Es wird hervorgehoben, dass die Kontrolle der Ausnützung der photographischen Chemikalien und des Filmverbrauches erleichtert wird.

RÉSUMÉ

Description d'une modification simple de l'appareil marqueur de films habituel qui permet de compter automatiquement les radiographies. Son emploi donne un meilleur contrôle de l'épuisement des solutions photographiques et celui des films radiographiques utilisés.

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THE PROGNOSTIC VALUE OF HISTOLOGIC GRADING OF CARCINOMA OF THE CERVIX UTERI

A Study of 388 cases treated with Radium and Roentgen therapy

by

F. Linell and *B. Månsson*

Introduction

During the last few decades histologic grading of carcinoma has become an increasingly common practice, particularly in the U. S. A. As to the prognostic value of such classification and its use in the choice of therapy, opinions differ widely. It does not sound unreasonable to suppose that the biologic characteristics of cancer will depend on its site and that conclusions concerning the prognostic value of the grading of cancer of one organ or system cannot be strictly applied to the grading of cancer situated elsewhere in the body. Many workers in this field have investigated the prognostic value of histologic grading of cancer of the cervix of the uterus but no unanimity has been attained.

The purpose of this article is to give a brief critical review of the relevant literature and to record the observations we have made in 388 cases of carcinoma of the uterine cervix.

Earlier Investigations

In their monograph on cancer of the uterus SCHOTTLAENDER and KERMAUNER (1912) classed their 144 cases as "reife, mittelreife and unreife" (mature, maturing and immature). As the patients were not followed up in the modern sense of the word, it is not possible to assess the prognostic value of histologic grading from the investigation.

Submitted for publication, March 7, 1952.

In the U. S. A. BRODERS is one of the foremost advocates of histologic grading of tumours. He distinguishes four grades (I—IV). In 1922 he reported 269 cases of carcinoma of the cervix uteri. In this series the patients had been operated on by various methods, and the prognostic value of histologic grading cannot be deduced from the tables given. Later, in 1926 he reported a second series consisting of 880 cases of "graded epitheliomas (squamous epithelial cancer, lip cancer)" but he made no particular mention of cancer of the cervix. He did not say how long the patients had been followed up or how they were treated, neither did he define what was to be understood by *good results*. For these reasons the prognostic value of histologic grading of cervical uterine cancer cannot be deduced from the works of BRODERS. This also applies to a later article which he published in 1941.

THIBAUDEAU and BURKE (1929), who used BRODERS' classification scheme in the grading of carcinoma of the cervix treated with radiation, found the grade of a tumour to influence the prognosis but slightly. Their series was, however, too small (28 cases) to permit of any definite conclusions.

JORSTAD and AUER (1933), who likewise use BRODERS' classification scheme, graded 148 cases of cervical carcinoma treated with radiation: they claimed that other factors such as the local spread of the tumour were of greater prognostic importance than the histologic grade.

MARTZLOFF (1923—1945) classed the tumours according to the preponderant type of cell (*spinal, transitional or fat spindle cells*). His histologic types coincide roughly with BRODERS' grades II—IV. In 1927 MARTZLOFF compared the results of histologic grading in small biopsy specimens and operative specimens obtained at subsequent hysterectomies. In one third (23/70) of the cases examined in this way the biopsy specimen differed from the operative specimen in the preponderant type of cell. This shows how misleading the use of small biopsy specimens can be. In order to find out whether the prognosis was related to the histologic grade of the cancer MARTZLOFF (1928) later studied 146 cases of cancer that had been followed up for 5 years after operation. Cures were claimed in 63.6 per cent of 30 cases of spinal cell cancer, in about 46 per cent of 90 cases of transitional cell cancer, in 14 per cent of 17 cases of fat spindle cell cancer and in 75 per cent of 9 cases of adenocarcinoma. These groups were too small to permit of any conclusions of statistical significance. He also stressed that factors other than the histologic grading are of prognostic importance. His figures refer to operated cases only.

Many workers in this field have employed grading systems more or less similar to that of MARTZLOFF. POMERY and STRAUSS (1924) studied 100 cases, but only 65 were followed up for 2 years or more. The series will not allow any conclusions as to the existence of any relationship

between prognosis and histologic grade. This also applies to PEMBERTON's (1926) series of 96 cases. KIMBROUGH and NORRIS (1927) and NORRIS (1935), who used MARTZLOFF's system, graded 120 cases treated with radiation and followed up for 5 years. Their observations did not suggest any relationship between the prognosis and the histologic grade of the cancer. This also holds good for MALIPHANT's (1933) series treated with radiation. Some of his cases were followed up for 3 years. GULIK (1939), who also used MARTZLOFF's classification system in a study of 180 cases treated with radiation and followed up for 5 years, found no certain difference in prognosis between the various histologic grades.

BÖHM and ZWEIFEL (1926) applied a completely different grading system for forecasting the course of the disease in a given case. Their series consisted of 122 cases treated with radiation in 1912—1913. At a reviewal (about 10 years later) they found the prognosis to have been correct in 92 cases but wrong in 30. They attached much importance to the amount of stroma but also took into account other factors such as the degree of maturity and the amount of mitoses. It is difficult to assess the value of this praiseworthy result because the series dates back to a period prior to the standardization of therapeutic methods.

In a series of 188 cases treated with radiation WARD and FARRAR (1926) found that the course of the disease could not be predicted satisfactorily by the histologic grade of the tumour. They gave no percentages.

FLUHMAN (1927), who used SCHOTTLÄNDER and KERMAUNER's system, stated that "evidence is given supporting the conception that immature forms do better with radium", but his series is too small to permit of any definite conclusions.

LACASSAGNE (1928) distinguished 3 types of carcinoma of the cervix, namely 2 grades of squamous cell carcinoma and adenocarcinoma. On the basis of 97 cases treated with radiation he concludes that "the histological character so important in other situations of cancer would appear to play only a secondary rôle in the results obtained by radiotherapy of cervical cancer in comparison with the part played by the quality of treatment".

HEALY and HEALY and CUTLER (1928—1935) reported the relationship they found between histologic grade and the results of treatment of carcinoma of the uterine cervix. They distinguished 3 grades closely corresponding to MARTZLOFF's grades and BRODERS' grades II—IV. 200 cases treated with radiation and followed up for 5 years were graded. The results showed that the prognosis depends on the combined effect of several factors and that the histologic type of the tumour is of only minor prognostic importance. They nevertheless held that, as far as advanced lesions are concerned, the prognosis of anaplastic cancer treated with radiation was more favourable than that of more differentiated tumours.

This assumption was, however, not supported by the observations made by WETTERDAL (1934) in a series of 354 cases of cervical cancer treated uniformly and followed up for 5 years. The cases were graded histologically in co-operation with REUTERWALL and by the same system as that used by HEALY and CUTLER. WETTERDAL claimed that the results suggested that "the histological picture in cervical cancer consequently does not, contrary to statements from other quarters, afford any prognostical guidance".

In 1927—1929 HUEPER and SCHMITZ presented a number of articles on the prognostic value of histologic grading. HUEPER criticized BRODERS' grading system: he said it was too subjective and that the results could not be reproduced by different researchers. HUEPER therefore devised a "malignancy index". A later elaboration of this method distinguished 20 different histologic or cytologic characteristics, each of which carried one or more points. The sum of these points allotted to a given case was said to be the malignancy index. At first sight the method seems to promise accuracy, but the number of points assigned to a given case must be subjective, and therefore it is difficult to evaluate the method. Another disadvantage of this system is that it is complicated and probably time-consuming. The value of this malignancy index could not be deduced from HUEPER's (1928) series, because the latter comprised only 58 cases treated with radiation and reviewed 3 years or more after treatment.

MORTON (1938) graded 160 cases treated with radiation. He stressed the number of factors capable of influencing the prognosis and summed up with "we do not believe that cell-type or mitosis content are of much significance in the determination of prognosis".

REICHENMILLER et al. (1947) reported 631 cases that had been followed up for 5 years. They divided the series into 7 different histologic groups. Despite the largeness of the series this division resulted in the groups being fairly small. Judging by their figures, the histologic grade of a tumour has no appreciable influence on the end-results.

KLEINE (1942) described 510 cases treated uniformly with radiation. He graded the cases by SCHOTTLÄNDER and KERMAUNER's system. His figures suggest that the prospects of a 5-year cure are greatest in cases of immature squamous epithelial carcinoma.

GILMOUR, GLÜCKSMANN and SPEAR (1949) reported 724 cases of solid cervical carcinoma that had been treated with radiation and had been followed up for 5 years at the Marie Curie Hospital, London. They classed the tumours as anaplastic (A-tumours) and squamous cell differentiating tumours (D-tumours). As to the frequency of 5-year cures, they found a statistically significant difference between A- and D-tumours. The difference was however not large. GLÜCKSMANN and SPEAR (1945) also studied the prognostic value of the reaction of the tumours during radiation as

reflected in biopsy specimens removed before and during treatment. The method is time-consuming, because differential cell-counts must be made. TAYLOR (1951) also points out that "massive radium necrosis renders the taking of a good second biopsy extremely difficult, and histological interpretation of tumour cell change is often impossible. Where, however, the biopsy is satisfactory, tumour changes are apparent. Cell counts, as practised by GLÜCKSMANN in the assessment of radium response are not possible in every case". It is still too early to judge the value of GLÜCKSMANN's method. It is, however, doubtful whether it will ever become a routine measure.

Summarizing then, it seems that most of the authors who studied the question in fairly large series followed up for a sufficient length of time did not find the histologic grading of tumours of the uterine cervix to be of any certain prognostic value. In those series in which later reviewal suggested that the prognosis differed with the type of cancer, the difference was usually small. In addition, contradictory views have been presented: some authors such as KLEINE claimed that anaplastic cancer treated with radiation has a better prognosis than more differentiated tumours while other workers such as GLÜCKSMANN and SPEAR, hold an opposite opinion.

Material and Methods

The histologically examined material consisted of biopsy specimens from 388 cases of cancer of the cervix. Most of the sections were routine preparations. Frozen sections were stained according to v. Gieson. Only a few of the sections were embedded in paraffin. Most of the preparations were small, and as they had been removed for diagnostic purposes they were not carefully chosen from the border of the tumour. Therefore the quality of the sections varied from one case to another. The purpose of the investigation was, however, to find out whether histologic grading of such diagnostic specimens was of prognostic value.

The grading was done by one of us (LINELL) and, so that the classification might be as uniform as possible, the sections were examined within a fairly short period. Some of the cases had to be excluded because the specimens were qualitatively or quantitatively unsatisfactory. Specimens removed after the commencement of radiation were likewise excluded. The grading was done without pre-knowledge of the clinical course.

The grading was, as usual, to a certain extent subjective. The method applied probably came closest to that described by ACKERMANN and REGATO. The cases were graded mainly by the degree of anaplasia. The classification principles adopted are described below. Solid (squamous cell) carcinomas were divided into three grades.

Grade I. The most differentiated tumours were assigned to this grade. These tumours are built up of large, fairly uniform cells. No nuclear monstrosities are seen and the mitoses are as a rule sparse. Horny pearls are fairly common. It should however be stressed that true cornification with the formation of keratohyaline granules is rare in carcinoma of the cervix. It is usually a question of parakeratotic pearls with preserved or partly preserved nuclei. These pearls stain in the same manner as keratin. Horny pearls

with keratohyaline granules are sometimes seen (4 of 364 cases of cancer examined). Co-existent para-keratotic pearls are usually present. Grade I included not only these cases but also other highly differentiated tumours showing no formation of horny pearls. In these the cells are as a rule smaller but uniform in size and in appearance. They are of a distinct squamous cell character with intercellular bridges (Figs. 2 and 3). The frequency of mitosis is as a rule rather low but areas with numerous mitoses may be seen.

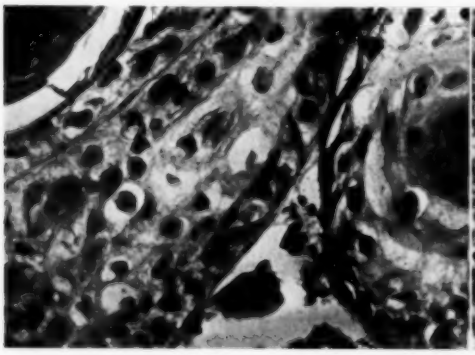

Fig. 1. Squamous cell cancer, Grade I. Large pale-staining cells. There are several horny pearls, but they are parakeratotic with preserved nuclei in the cells.

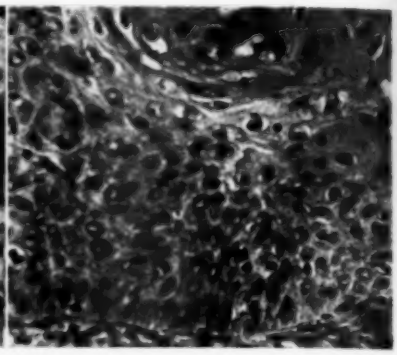

Fig. 2. Squamous cell cancer, Grade I. Distinct squamous cell characteristics. At the top — signs of a tendency to pearl formation, with large pale-staining cells but no true horny pearls. Scattered mitoses are to be seen.

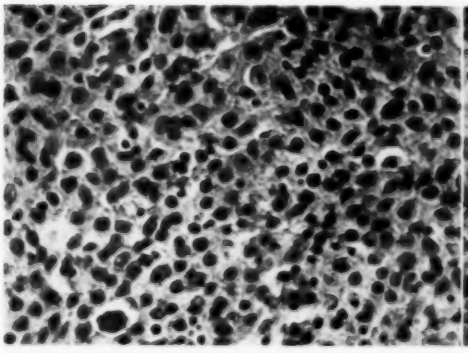

Fig. 3. Squamous cell cancer, Grade I. Uniform cells without tendency of pearl formation. Mitoses are rather sparse.

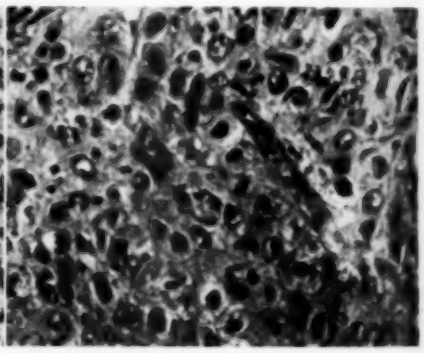

Fig. 4. Squamous cell cancer, Grade II. The cells are somewhat polymorphous and numerous mitoses are to be seen; many of the cells, however, show distinct differentiation.

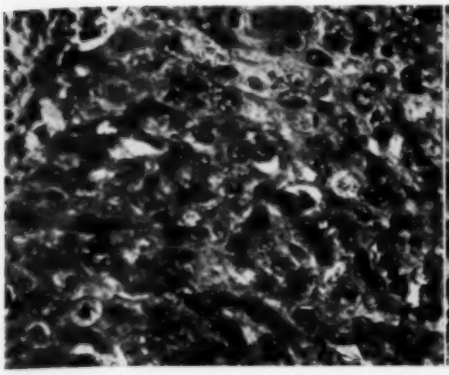

Fig. 5. Squamous cell cancer, Grade II. Basophilic, highly anaplastic cells with numerous mitoses. A tendency to pearl formation of typical prickle cells is, however, observable.

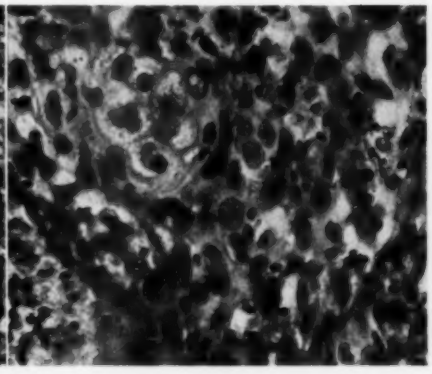

Fig. 6. Squamous cell cancer, Grade II. The cells are highly anaplastic with nuclear monstrosities; more differentiated cells, however, are also seen.

Grade II. Cases in which anaplasia was fairly obvious were assigned to this group. As a rule the cells vary in size and shape and mitoses are usually numerous. For a relatively anaplastic tumour to be classed as grade II it had to contain signs of the differentiation with large, pale staining cells showing the characteristics of squamous cells (intercellular bridges) in at least part of the preparation (Figs. 4—6). Carcinomas of this grade often show a tendency to pearl formation but cornification is uncommon. In the present series it was seen in a few isolated cases where a few scattered parakeratotic

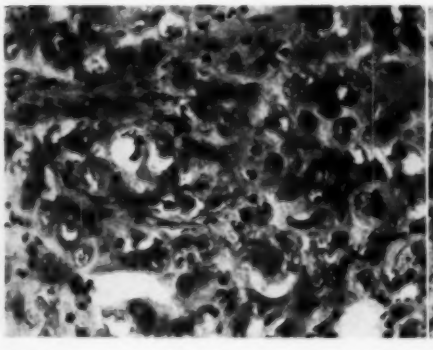

Fig. 7. Squamous cell cancer, Grade III. Wholly undifferentiated cells with marked anaplasia and numerous, often atypical, mitoses. Nuclei are large and polymorphous.

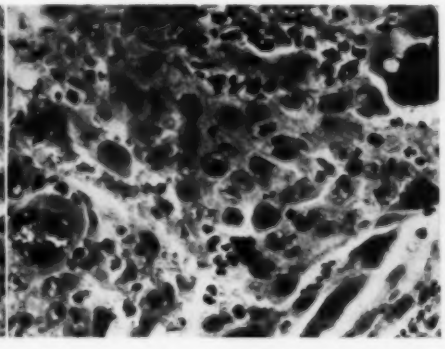

Fig. 8. Squamous cell cancer, Grade III. Highly polymorphous cells with several multinucleated giant cells. Obvious hyperchromatism in many cells.

pearls were found. This group also comprised tumours that were highly anaplastic and contained large multinuclear cells provided they nevertheless showed a tendency to differentiation. Grade II was the largest group in the present material.

Grade III. Tumors showing fairly distinct anaplasia were allotted to this group. In these cases the characteristics of squamous epithelial cells could no longer be recognized. This group comprises those cases with the most striking nuclear monstrosities and usually with numerous mitoses. In this type of tumour no signs of a tendency to differentiation are seen (Figs. 7—8). Carcinoma built up of fairly uniform elongated cells with basophilic cytoplasm and hyperchromatic nuclei (Fig. 9) are also referred to this grade. This latter type probably coincides roughly with what MARTZLOFF classes as tumours with "fat spindle cells".

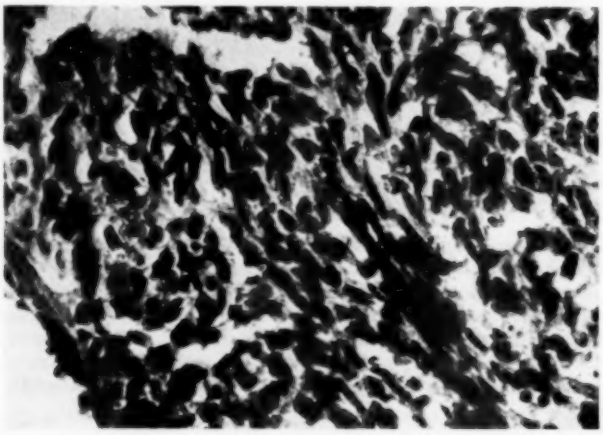

Fig. 9. Squamous cell cancer, Grade III. Rather small elongated cells with hyperchromatic nuclei and numerous mitoses. No signs of differentiation.

No attempts were made to grade adenocarcinoma of the cervix, because the group in the present series was too small. Most of the adenocarcinomas were fairly anaplastic, though variations were seen. In some cases the tumour contained solid structures (Fig. 10).

As to the squamous cell carcinomas it should be stressed that the various grades cannot be clearly defined: they were classed by the general impression gained on examination of the preparation as a whole. Owing to the vague line of distinction between the different grades it was often difficult to say to which grade a tumour should be assigned.

The preparations were also examined separately for a few other features. The frequency of mitosis was assessed, and the amount of parenchyma in proportion to that of the stroma was estimated. The tumours were then grouped in three different categories, namely

1. Ample stroma, *i. e.* more stroma than parenchyma,
2. Moderate stroma, *i. e.* roughly the same amount of stroma as parenchyma,
3. Sparse stroma, *i. e.* more parenchyma than stroma.

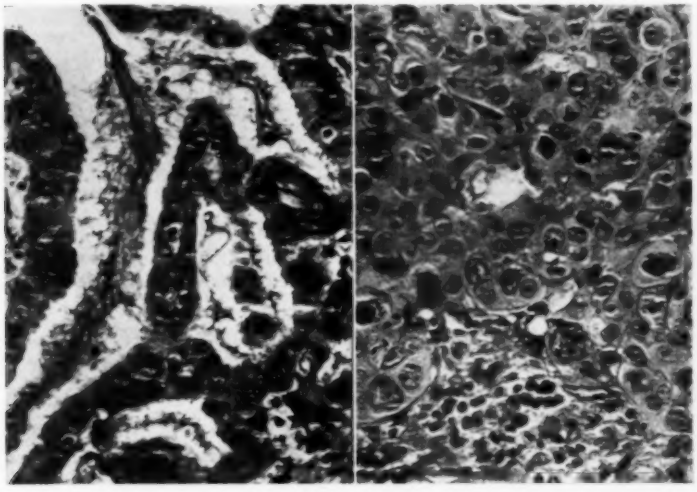

Fig. 10. Adenocarcinoma. To the left, a part of the tumour with anaplastic adenocarcinomatous structures. To the right, another part with solid tumour-proliferations. There are numerous mitoses.

This classification method is of course crude, especially as the amount of parenchyma in proportion to that of the stroma can vary widely from one part to another even in a small biopsy specimen.

The cellular reaction of the stroma was also estimated and the cases divided into three groups accordingly.

1. Strong reaction of the stroma, *i. e.* compact infiltration of the stroma so that the connective tissue was almost completely concealed by inflammatory cells.
2. Moderate reaction of the stroma, *i. e.* fairly abundant cellular infiltration, but not so profuse that the connective tissue could not be seen in at least some areas.
3. Sparse reaction of the stroma, *i. e.* scattered cellular infiltration in the connective tissue.

This classification is likewise crude, and it was sometimes questionable to which group a case should be assigned. Moreover, the reaction of the stroma often varied from one part of the preparation to another.

Finally the types of cells partaking in the reaction of the stroma were also noted and the cases grouped accordingly into three categories, namely

1. Mainly round cells in the stroma.
2. Mainly polymorphonuclear leucocytes in the stroma.
3. Roughly equal amounts of the two above-mentioned cell types.

The classification of the tumours by these criteria is of course unreliable because the type of cellular reaction often varies widely from one part of the preparation to another.

Results

All the cases examined had been treated at King Gustaf V:s Jubilee Clinic, Lund in 1935—43. As mentioned in an earlier section, some of the cases were excluded because the preparations were qualitatively or quantitatively unsatisfactory or because the biopsy specimens had been removed after the commencement of radiotherapy.

This left 388 cases. Of these, 24 were adenocarcinomas and 364 squamous epithelial carcinomas. The latter group included 7 cases of stump-cancer (cancer of the residual part of the uterine cervix after supravaginal amputation of the uterus).

As to treatment, only 291 of these remaining 357 cases received a *complete* course of radiotherapy consisting of 3 radium applications (intra-uterine and vaginal) at intervals of 1 and 3 weeks respectively. At every application, which lasted 20 hours, a dose of 900 mgh was delivered intra-uterinely and 1,500 mgh intra-vaginally.

These patients thus received 3×900 mgh $= 2{,}700$ mgh intra-uterinely and $3 \times 1{,}500$ mgh intra-vaginally. As to the intra-uterine dose, it varied in a few single cases but always lay within the range of 2,600 mgh—2,800 mgh. In a few exceptional cases the vaginal dose varied by at the most $\pm$ 300 mgh.

Apart from these few minor deviations, it may be said that the total dose delivered was 7,200 mgh.

The course also included roentgen therapy, as a rule 3×400 r $=$ $=$ 1,200 r against each of 2 anterior and 2 posterior parametric fields. (170 KV, distance 40 cm, filter 0.5 mm Cu and 1 mm Al, the field varying in size from 100—200 cm² according to the stature of the patient.) Roentgen treatment was given during the intervals between the Ra-radiation.

After subtraction of the adenocarcinomas the remaining 357 cases fell within the histologic groups as follows:

Table I

Histologic grades	Incomplete treated	Complete treated	Total	Per cent
I	20	63	83	23.3
II	36	167	203	56.8
III	10	61	71	19.9
	66	291	357	100.0

The *age distribution* of the histologic groups is summarized in the following table.

If the number of cases in each age-group be expressed as a percentage of the total number of cases in the respective histologic groups and these

Table II

Age	Histologic grades I	II	III
20—25 years	1	3	
25—30 »	1	5	3
30—35 »	9	14	5
35—40 »	7	21	9
40—45 »	12	25	7
45—50 »	14	30	7
50—55 »	12	26	16
55—60 »	7	29	10
60—65 »	6	18	6
65—70 »	5	21	5
>70 »	9	11	3
Total	83	203	71

percentages be plotted, the curves will run fairly parallel and no significant difference will be seen between them.

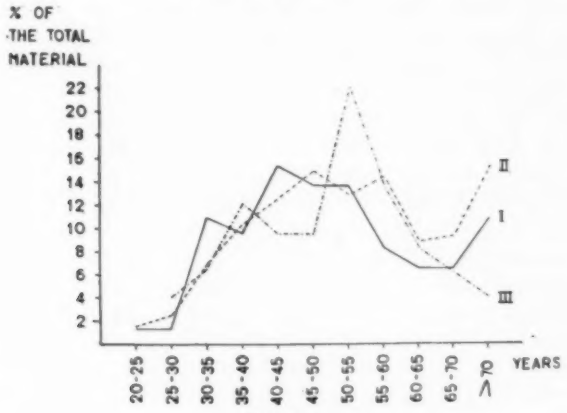

Fig. 11.

The histologic groups varied but slightly from one another as regards the number of pregnancies the women had had.

Table III

Histologic grades	Average pregnancies per case
I	3.0
II	3.1
III	3.1

The history of the lesions, as reckoned from the onset of the initial symptoms — usually irregular bleeding — did not vary appreciably in

length from one histologic group to another, as will be apparent from the following table.

Table IV

Length of history in months	Histologic grades I	II	III
0— 3	26	69	21
3— 6	41	71	20
6—12	14	50	20
>12	2	13	10
Total	83	203	71

In order to obtain comparable values of possibly important prognostic factors, only those 291 cases that had received a complete course were included.

The tumours are classed according to local spread by the scheme recommended by the League of Nations. All of these cases received radiotherapy at the Gynecological Department of King Gustav V's Jubilee Clinic, Lund, where the patients were also followed up. The patients were always reviewed by the same examiners. All the patients were re-examined 1 month after the last Ra-radiation. If they were doing well, they were not reviewed again until after a further 2 months. The interval between the reviewals was then gradually increased to 3—4 months. Those patients who had a 5-year cure were no longer requested to present themselves for routine reviewal. They reported their state of health and any symptoms by letter every 6 months, later every year, and were only requested to present themselves for examination if symptoms of a recurrence had appeared.

The frequencies of 5-year-cures in the various clinical stages and histologic groups were as follows. The figures in brackets give the number of 5-year-cures.

Table V

Clinical stage	Histologic grade I		I		III		Total		Per cent 5-year-cures
I	9	(2)	21	(15)	10	(5)	40	(22)	55 ± 7.9
II	26	(11)	83	(37)	25	(14)	134	(62)	46.3 ± 4.3
III	25	(17)	53	(13)	20	(6)	98	(36)	36.7 ± 4.9
IV	3	(1)	10	(3)	6	(0)	19	(4)	21.1 ± 9.4
Total	63	(31)	167	(68)	61	(25)	291	(124)	42.6 ± 2.9
Per cent 5-year-cures ...	49.2 ± 6.3		40.2 ± 3.8		41.0 ± 6.3		42.6 ± 2.9		

It will be apparent from the table that the histologic grades were distributed equally among the various clinical stages. The frequency of 5-year-cures did not differ statistically significantly from one histologic group to another.

Cornification occurred in 31 cases (4 with true cornification + pseudo-cornification and 27 only pseudo-cornification) in grade I. Of these 31 cases with cornification 14 (about 45 per cent) have been given 5-year-cures. Among the remaining 32 cases without cornification were 17 (about 53 per cent) 5-year-cures. This suggests that cornification does not influence the prognosis. (Grade II group comprises 9 cases with pseudo-cornification. Of these, 5 had been given a 5-year-cure.)

The amount of mitoses seen in the tumours is summarized in the following table.

Table VI

Histologic grade	Amount of mitoses			Total
	Numerous	Moderate	Sparse	
I	15	32	16	63
II	144	22	1	167
III	51	9	1	61
Total	210	63	18	291
Corresponding 5-year-cures	89	27	8	124
per cent	42.4 ± 3.4	42.9 ± 6.3	44.4 ± 11.7	42.6 ± 2.9

The amount of mitoses in the tumour thus seems to be of no prognostic importance.

The relative quantity of stroma noted in the tumours is given in the following table.

Table VII

Histologic grade	Quantity of stroma			Total
	Ample	Moderate	Sparse	
I	14	23	26	63
II	39	63	65	167
III	14	25	22	61
Total	67	111	113	291
Corresponding 5-year-cures	32	50	42	124
per cent	47.8 ± 6.5	45.0 ± 4.7	37.1 ± 4.5	42.6 ± 2.9

Thus no statistically significant differences were found.

The following table summarizes the cellular reaction of the stroma in the various histologic groups.

The figures suggest that a scanty cellular reaction of the stroma may be a sign of a poorer prognosis, but this assumption was not supported by any statistically significant difference.

Table VIII

Histologic grade	Cellular reaction of the stroma			Total
	Strong	Moderate	Sparse	
I	21	28	14	63
II	70	74	23	167
III	36	16	9	61
Total	127	118	46	291
Corresponding 5-year-cures	56	53	15	124
per cent	44.1 ± 4.4	44.9 ± 4.6	32.6 ± 6.9	42.6 ± 2.9

The type of cellular infiltration will be apparent from the following table.

Table IX

Histologic grade	Mainly round cells	Mainly polymorpho-nuclear leucocytes	Roughly equal number round cells and p. n. leucocytes	Total
I	41	5	17	63
II	120	10	37	167
III	38	4	19	61
Total	199	19	73	291
Corresponding 5-year-cures	90	4	30	124
per cent	45.4 ± 3.5	21.1 ± 9.4	41.5 ± 5.7	42.6 ± 2.9

It is known that infection of the tumour will worsen the prognosis (HUEPER, 1928). The relatively poorer results achieved in the group in which the cells in the stroma were preponderantly polymorphonuclear leucocytes also suggests, though not with statistical significance, that such infection tends to worsen the outlook. It was also observed, however, that the local spread of the tumour in the 19 cases of this group was fairly extensive; only 1 of them belonged to stage I, 5 to stage II, while 10 belonged to stage III and 3 to stage IV.

The series was also studied for any prognostic effect of cornification, relative amount of stroma, the reaction of the stroma, the amount of mitoses and cellular infiltration respectively in relation to the age of the patients in the various age-groups. The results did not suggest that the effects varied with age.

As mentioned in an earlier paragraph, the 24 cases of adenocarcinoma were not histologically graded. Of these, 18 received a *complete course* of radiation and in 7 of them five-year cures were obtained. Such cures were achieved in altogether 8 of the 24 cases.

Discussion

It is known from earlier investigations that the prognosis of carcinoma of the uterine cervix is dependent on many factors, one of the most important of which is the local spread of the tumour. But the clinical course of tumours of fairly equal local spread is also known to vary widely from one case to another, and many attempts have been made to find an explanation for this variation. Attention has been directed mainly to the histologic and cytologic properties of the tumours in the hope that this might reveal the cause. However, the present investigation, like most of the earlier work in this field, failed to show any certain relationship between the histologic structure and the prognosis. This agreement is probably mainly ascribable to the fact that the histologic structure of carcinoma of the uterine cervix, like that of tumours in many other parts of the body, reveals but little of the biologic character of the growth. It is also known that a small biopsy-specimen will not always show a representative picture of the tumour (MARTZLOFF), for the dominating type of cell may vary from one part of the growth to another. It is, however, debatable whether it is theoretically correct to grade a tumour according to the dominating type of cell. BRODERS' and MARTZLOFF's grading systems are based mainly on this characteristic feature. But no evidence is available to exclude the possibility that the biologic properties of the tumour are determined by the most undifferentiated cells, no matter whether they are preponderant or not. Should this be the case, all cervical cancer would be of one and the same grade, for highly undifferentiated cells are always to be seen along the margins of the cancer cell columns. This would also explain why the various grades of tumour did not vary as regards prognosis.

It has, however, also been suggested that the tendency of the cells to differentiate towards a higher degree of maturity may be of prognostic importance. The grading system used in the present study was also based on this assumption. For example, all cases in which a tendency to conversion into higher differentiated cells despite the presence of a marked preponderance of strongly anaplastic cells was noticed, were assigned to grade II.

However, the investigation failed to provide an explanation for the point under discussion, for the various grades were not found to differ as regards prognosis. This may be due to the fact that the examination of small biopsy specimens that had not been carefully selected or removed by one and the same method throughout did not reflect a true picture of the tendencies of the tumours to differentiate. It is possible that we could have obtained better results if we had adopted GLÜCKSMANN's method

and examined biopsy specimens removed during radiation therapy. The method requires biopsy specimens removed on at least two occasions, and this is not always possible (TAYLOR). It seems clear that a simple grading of the tumours by the types of cells found in a single small diagnostic biopsy specimen is of no prognostic value in cases to be treated with radiation.

The estimated relative frequency of mitoses seemed to have no influence on the prognosis in the present series. Neither was any such influence expected, for it is known that the frequency of mitoses varies from one part of tumour to another. Moreover, the frequency of mitoses is probably no reliable measure of the degree of malignancy of a tumour.

It has also been discussed whether the response to radiotherapy wil depend on the relative amount of stroma. We studied the amount ol stroma and the density of the infiltration of inflammatory cells in the stroma, but neither of these factors seemed to influence the prognosis. In the group with sparse cellular infiltration (table VIII) the results achieved by radiotherapy were less favourable than in the other groups, but the difference was not statistically significant, and is, in our opinion, not important. We also studied the type of the inflammatory cells in the stroma (table IX). In the group in which the cells in the stroma were preponderantly polymorphonuclear leucocytes the frequency of 5-year-cures was lower than in the other groups. An ample amount of polymorphonuclear leucocytes suggests ulceration and infection of the tumour, and it has been held (HUEPER) that this worsens the prognosis. Our series is too small and too heterogeneous to permit any conclusions for or against this view.

Summarizing, most of the observations made suggest that the simple grading of tumours on the basis of diagnostic biopsy-specimens is of no prognostic value. Some authors who have studied the problem in large series came to the opposite conclusion. According to KLEINE, for example, the undifferentiated squamous epithelial cancer had the best prognosis, while GLÜCKSMANN and SPEAR are of the opinion that the more mature squamous epithelial cancer responds best to radiation. These contradictory opinions may be ascribable to differences in material and treatment but may also be due to chance.

The observations made in the present investigation thus suggest that the prognosis of cancer to be treated with radiation cannot be deduced from examinations of small diagnostic biopsy-specimens: this despite the fact that all of the preparations in the present series were examined by one and the same person and during a fairly short period. The following objections may be raised against histologic grading as a routine method. As stressed by HUEPER and others, grading must be subjective and will therefore vary to a certain extent from one pathologist

to another. This must surely diminish the value of histologic grading as a routine method, for the grading will probably be done by more than one pathologist, at least at large hospitals. But even here opinions differ. Independently of one another JORSTAD and AUER (1933) graded 300 cases of cervical cancer by the system of BRODERS, but in only 1 per cent of the cases was there lack of agreement. This figure seems to be very low. Further discussion of this point is, however, of no interest until it can be proved that histologic grading really is of prognostic value.

Broadly speaking, it is difficult or impossible to predict the further course of a given case of cancer of the cervix treated with radiation. The prognosis probably depends on a number of still unknown or immeasurable factors. NORRIS (1935) pointed out that the radiosensitivity of a tumour depends on the extent to which it is accessible to radiation, on the immediately surrounding tissue, on its vascularity and the general condition of the patient, the degree of anaemia and other factors. Other factors of importance are *e. g.* hereditary predisposition, the nature of the vaginal flora and earlier or co-existent diseases. In studies of cancer elsewhere in the body, it has been observed that the growth is influenced by the sex glands and the hormones produced by them. Therefore it does not sound unreasonable to suppose that the course of carcinoma of the uterine cervix will also depend to a certain extent on the endocrine status of the patient. All of these possible influences, singly or in combination, are still difficult to measure or to record numerically and must therefore be left to later research.

SUMMARY

309 cases of carcinoma of the cervix uteri treated uniformly with radiation and followed up for at least 5 years were examined. Of these cases 291 were squamous cell carcinomas and 18 were adenocarcinomas. Treatment consisted of radium and roentgen therapy. Of the patients who received a complete course 42.6 per cent became 5-year-cures.

The material examined consisted of diagnostic biopsy specimens and the grading and other histologic details were noted without pre-knowledge of the later course of the disease. The cases were classed according to three grades, which are described in detail. The amount of mitoses and stroma as well as the intensity of the reaction of the latter and its cellular type were also recorded.

The cases allotted to the various groups according to grading or other histologic characteristics did not differ significantly as regards prognosis. The results were on the whole in accord with those obtained by earlier workers in this field and suggest the conclusion that the histologic grading of carcinoma of the cervix uteri from diagnostic biopsy specimens is of no value for predicting the prognosis of cases to be treated with radiation.

ZUSAMMENFASSUNG

309 Fälle von Carcinoma colli uteri, die einheitlich bestrahlt und mindestens 5 Jahre lang beobachtet worden sind, wurden untersucht. Von diesen waren 291 Fälle Platten-

epithelcarcinome und 18 Fälle Adenocarcinome. Die Behandlung bestand aus Radium- und Röntgenterapie. Fünfjahresheilung erhielt man in 42.6 % aller vollständig behandelten Fälle.

Das untersuchte histologische Material bestand aus Biopsien, die zu diagnostischen Zwecken vorgenommen wurden und die histologische Gradierung sowie die übrigen histologischen Daten sind ohne Kenntnis der Prognose registriert worden. Eine Aufteilung in 3 Gruppen, über die aufs genaueste berichtet wird, ist geschehen. Weiteres wurde besonders der Mitosenreichtum, die Menge des Stromas, die Intensität der Stromareaktion sowie der Zelltyp des Stromas registriert.

Prognostisch signifikative Unterschiede hinsichtlich der Gradierung und der übrigen untersuchten Verhältnisse sind nicht gefunden worden. Die Ergebnisse stimmen im grossen Ganzen mit denen früherer Untersucher überein und berechtigen zu der Schlussfolgerung, dass die histologische Gradierung von zu diagnostischen Zwecken vorgenommenen Probeexcisionen von Collumcarcinomen keinerlei prognostischen Wert für die Strahlenbehandlung haben.

RÉSUMÉ

Les auteurs ont étudié 309 cas de cancer du col de l'utérus traités uniformément par radiothérapie et suivis pendant au moins 5 ans. Parmi eux se trouvaient 291 cas d'épithélioma pavimenteux et 18 cas d'adénocarcinome. Le traitement a consisté en curie- et roentgenthérapie. 42.6 % des malades qui avaient subi le traitement complet ont présenté une guérison de 5 ans.

Le matériel examiné consistait en préparations biopsiques, et le stade et les autres détails histologiques ont été déterminés sans qu'on ait connaissance de l'évolution ultérieure de la maladie. Les cas furent classés en trois stades qui sont décrits en détail. Le nombre des mitoses, l'importance du stroma ainsi que l'intensité de sa réaction et son type cellulaire ont aussi été enregistrés.

Les cas répartis dans les divers groupes suivant leur stade et leurs autres caractères histologiques n'ont pas eu un pronostic notablement différent. Les résultats ont dans l'ensemble concordé avec ceux des autres auteurs et conduisent à conclure que la classification histologique des cancers du col de l'utérus d'après les examens biopsiques n'a aucune valeur pour porter un pronostic sur les cas qui doivent être traités par radiothérapie.

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SERVICE DES RECHERCHES EXPÉRIMENTALES (DR. S. NEUKOMM) DU CENTRE ANTI-CANCÉREUX ROMAND, LAUSANNE (SUISSE)

CONTRIBUTION A L'ÉTUDE DU PHOSPHATE DE CHROME RADIOACTIF UTILISÉ POUR LE TRAITEMENT LOCAL DES TUMEURS

par

S. Neukomm, P. Lerch, Mme *L. Péguiron* et Mme *M. Richard*

A la suite des travaux de JONES et al., de ALLEN et al. et de HERVE et GOVAERTS, il nous a paru intéressant d'étudier à nouveau le comportement des tumeurs traitées in loco par le phosphate de chrome radioactif (P^*O_4Cr). Les problèmes à résoudre étaient les suivants:

a) y a-t-il inhibition du développement ou éventuellement destruction des tumeurs dans lesquelles est introduite la suspension de P^*O_4Cr?

b) le P^*O_4Cr reste-t-il localisé ou diffuse-t-il dans l'organisme?

Pour répondre à ces questions, trois séries d'expériences ont été faites in vivo et in vitro.

Injection de P^*O_4Cr dans des tumeurs spontanées de la Souris

10 femelles de la Souche R_3 présentant des tumeurs spontanées (adénocarcinome mammaire) de la grosseur d'une petite noisette sont traitées de la manière suivante: on injecte dans les tumeurs 0.1—0.15 cc d'une suspension de PO_4Cr stabilisée par de la gélose (1 cc de sol. de gélose à 1 % dans 10 cc de suspension de PO_4Cr). La suspension de PO_4Cr est obtenue suivant la technique de Herve et Govaerts. 1 cc de cette suspension contient 50 micro-curies, chaque tumeur injectée contient donc au moins 5 micro-curies (0.005 mc). 2 animaux sont sacrifiées 6 jours, 12 jours et 42 j. après l'injection pour l'étude histologique et autohistoradiographique des tumeurs. Les autres animaux meurent spontanément dans la période du 12e au 42e jour.

Soumis à la Rédaction le 19 Mars 1952.

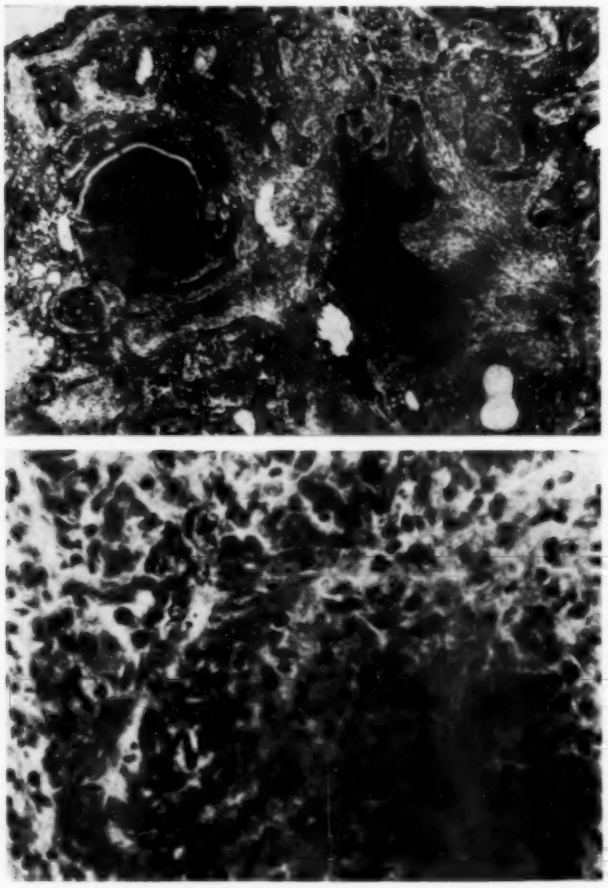

Fig. 1. Les dépôts de $CrP^{*}O_4$ sont représentés par les zones très foncées. Noyaux pycnotiques dans la région du dépôt (b); ailleurs pas de lésions reconnaissables.

A l'autopsie on prélève la tumeur injectée, les métastases, le foie, la rate, les ganglions. Le dépôt de PO_4Cr est facilement reconnu grâce à sa coloration verte.

Dans aucun cas, il n'y a eu de régression des tumeurs qui ont continué de se développer rapidement et de produire des métastases ganglionnaires (axillaires, inguinales, vulvaires). Le PO_4Cr est toujours resté parfaitement localisé à la tumeur injectée. Comparativement aux tu-

meurs non traitées, les tumeurs injectées ont présenté des nécroses centrales plus importantes et plus rapides.

L'examen microscopique ne montre pas de lésions destructives du foie, de la rate ou des ganglions. Dans les tumeurs, le matériel radioactif est enrobé dans les produits nécrotiques de la partie centrale non vascularisée. Il n'y a pas de destruction tissulaire à distance; l'action des radiations semble s'exercer dans une zone n'excédant pas une profondeur de 15—20 μ autour du dépôt de PO_4Cr ainsi qu'il ressort de l'examen des autohistoradiographies (fig. 1).

Elimination urinaire de P* chez des animaux traités par P^*O_4Cr

4 Rats mâles adultes reçoivent chacun 0.5 cc de la suspension stabilisée de PO_4Cr, c'est-à-dire une dose de 25 μc par animal. L'injection est faite dans le tissu cellulaire sous-cutané de la région ventrale médiane. Les animaux sont placés dans une cuve de verre sur un double treillis permettant de retenir les fèces. Après 5, 12, 19 et 26 jours on retire les animaux et on lave soigneusement la cuve. Les liquides de lavage sont alors concentrés par évaporation pour les mesures d'activité. Un étalon de comparaison a été préparé avec 0.5 cc de la suspension injectée dilué dans 500 cc d'eau distillée + 5 cc HCl conc. Les mesures d'activité ont donné les chiffres suivants:

No. jours après injections	Élimination en % dose administrée
5	0.36
12	0.11
19	0.05
26	0.04

L'élimination du P* dans ces conditions suit une loi exponentielle (fig. 2) dont la période est de 42 jours. En 26 jours, 0.56 % de la dose totale de P* administrée a été éliminée.

Réaction d'échange P^*O_4Cr/PO_4

Cette étude a été faite en vue de déterminer si l'élimination urinaire de P* après injection sous-cutanée de P^*O_4Cr était conditionnée par une réaction d'échange purement chimique entre les ions PO_4 de l'organisme et la molécule de PO_4Cr ou si elle était le résultat plus complexe d'une action hydrolysante des tissus sur la molécule de PO_4Cr.

La réaction étudiée est la suivante:

$$P^*O_4Cr + PO_4^{---} \rightleftharpoons PO_4Cr + P^*O_4^{---}$$

Le phosphate de chrome est mis en présence d'une solution tampon composée de 18.2 % KH_2PO_4 M/15 et de 81.8 % de Na_2HPO_4 M/15. Le PH est 7.4. La quantité de PO_4 de la solution est équivalente à celle de $CrPO_4$: (0.068 g $CrPO_4$ dans 4 cm³ sol. tampon).

La solution contenant le $CrPO_4$ est agitée deux fois par jour, filtrée 2 fois sur bande bleue et laissée à décanter une nuit, après 0, 1, 2, 4, 7, 10, 14, 21 jours.

Un étalon de comparaison est préparé avec 0.068 g $CrPO_4$ broyé très finement en suspension dans 100 cm³ d'eau distillée.

La mesure à 0 tient compte des particules de $CrPO_4$ restées en suspension.

Résultats: nos résultats sont condensés dans la fig. 2 et le tableau suivant:

Temps (jours)	% PO_4 échangé *
0	0
1	0.22
2	0.36
4	0.45
7	0.72
11	0.84
15	1.08
21	1.27

* moyenne de 2 déterminations

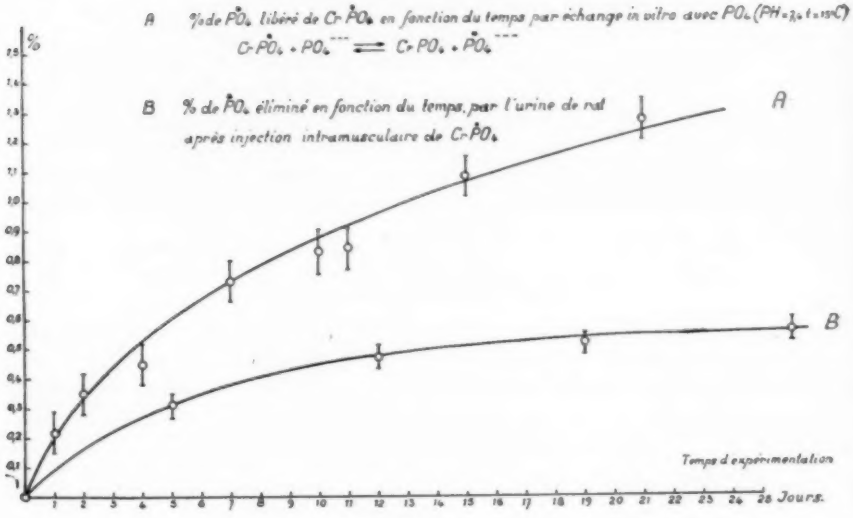
A % de P*O4 libéré de Cr-P*O4 en fonction du temps par échange in vitro avec PO4 (PH=7,4 t=15°C)
Cr-P*O4 + PO4''' ⇌ Cr-PO4 + P*O4'''
B % de P*O4 éliminé en fonction du temps, par l'urine de rat après injection intramusculaire de Cr-P*O4
A
B
%
Temps d'expérimentation
Jours.

Fig. 2.

Discussion

En conclusion de leurs recherches avec le PO_4Cr HERVE et GOVAERTS ont suggéré que »les applications locales peuvent également être envisagées car il semble n'y avoir aucune diffusion de colloïde». Nos expériences, comme celles de ALLEN et coll., confirment l'opinion que le PO_4Cr ne diffuse pas lorsqu'il est déposé dans du tissu carcinomateux ou dans le tissu cellulaire sous-cutané. Les doses radioactives utilisées dans nos recherches ne sont pas suffisantes pour entraîner une destruction notable du tissu carcinomateux, et ceci malgré la »concentration» relativement très grande du rayonnement donné sous forme de suspension insoluble. ALLEN et coll., en injectant des quantités plus importantes de matériel radioactif dans le tissu péritumoral, ont obtenu des régressions complètes des tumeurs. Ils ont observé que la dose maximale tolérée par une Souris était environ 1 mc. Ils font remarquer que la dose optimale nécessaire pour obtenir une régression des tumeurs dépend du volume de la tumeur et de son type histologique. Pour l'adénocarcinome spontané de la mammelle, transplanté sur la souche C57, les meilleures conditions thérapeutiques sont réalisées lorsque le poids de la tumeur est plus petit que le 1/5 du poids du corps; au delà, la nécrose et l'infection surajoutées empêchent une survie prolongée malgré le traitement. Ainsi, l'application locale péri- ou intra-tumorale du P^*O_4Cr se heurte à certaines difficultés qui limitent son emploi en clinique.

L'étude de l'élimination urinaire du P* chez les animaux traités par le P^*O_4Cr ainsi que l'étude de la réaction d'échange $PO_4/Cr\,P^*O_4$ montrent que le P* du P^*O_4Cr se détache lentement de la molécule et passe dans les tissus et dans les urines. La quantité de P* éliminée dans l'urine est probablement 2 fois plus faible que la quantité libérée par échange dans les tissus. Ceci indique que le 50 % environ du P* est retenu dans l'organisme pendant un certain temps. Cette rétention prolongée de faibles quantités de P* pourrait être un facteur favorable supplémentaire dans le traitement des affections néoplasiques du système hématopoïétique par le P* administré sous forme de P^*O_4Cr.

RÉSUMÉ

On étudie histologiquement l'action du dépôt intratumoral de P^*O_4Cr, l'élimination urinaire du P* après injection sous-cutanée de P*OCr et la réaction d'échange PO_4Cr/P^*O_4. On discute l'utilisation du P^*O_4Cr en clinique.

SUMMARY

A histologic investigation on the intra-tumoral deposit of P^*O_4Cr, the urinary excretion of P* following the subcutaneous injection of P*OCr and the formation of PO_4Cr/P^*O_4, is described. The clinical employment of P^*O_4Cr is discussed.

ZUSAMMENFASSUNG

Eine histologische Untersuchung über die Wirkung der intratumoralen Deponierung von P^*O_4Cr, über die Ausscheidung des P^* im Harn nach subkutaner Injektion von P^*OCr und über die Austauschreaktion PO_4Cr/P^*O_4 wird beschrieben. Die klinische Anwendbarkeit von P^*O_4Cr wird diskutiert.

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BOOK REVIEWS

MALIGNANT DISEASE AND ITS TREATMENT BY RADIUM. Vol. IV. 2nd Edition. By Sir Stanford Cade. 544 pp. 785 illustrations. John Wright & Sons Ltd, Medical Publishers Bristol 1952. 63 shillings.

This part of Cade's well-known book deals with malignant disease of the skin, kidney, testis and prostate, with bone sarcoma, sarcoma of soft tissue, tumours of lymphoid tissue, and with the leukaemias and intracranial tumours. One obtains abundant and comprehensive up to date information regarding the clinical aspect and treatment of these conditions. The book thus does not deal only with radium treatment as the title suggests but the choice of treatment is discussed for each disease.

Cade, himself a surgeon, is a strong advocate of intimate liaison between the surgeon and the radiotherapist in the treatment of malignant tumours. Combinations of treatment has been the rule rather than the exception in Cade's own cases.

A detailed analysis of cases and illustrative case histories, of great value to every radiotherapist, appear at the end of each chapter.

An enormous amount of work and great experience lies behind this volume and it is warmly recommended to all students of malignant disease.

F. Jacobsson.

RADIOLOGIC PHYSICS. Second Ed. By Charles Weyl and S. Reid Warren Jr. XX + 491 pages. Charles C. Thomas, Springfield, Ill., 1951. $ 10.50.

The scope and diversity of the modern subject, Radiophysics, is well brought out by this book, covering a wide range of fields, as is evident from the following abridged Table of Contents: Discussion of scientific method — The experimental basis of electromagnetism — The quantitative analysis of electric circuits — Electrical measuring instruments — Transformers, generators and motors; electric power distributing systems — Principles of electronics — Electronic devices — High-voltage generators for X-rays equipment — The theory of radiant energy — X-rays and matter — Radioactivity and nuclear physics — The measurement and control of X-rays and radioactive emissions — Physical aspects of therapeutic and tracing techniques; equivalent dose for roentgen and radioactive emissions; protection — Physical aspects of fluoroscopic and roentgenographic techniques — The effects of variations of exposure factors on roentgenographic results — Appendix: Elements of algebra, trigonometry and calculus; mathematical tables.

The book presupposes in the reader very little preliminary knowledge of physics and mathematics; hence the need for a mathematical appendix and for much of the elementary physics in the first chapters. In the reviewer's opinion, however, such readers would need, before beginning with radiophysics, a much more thorough course in elementary general physics than it is possible to give in the limited space of the introductory chapters. The subject matter is therefore often treated rather superficially at the risk of making beginners believe things to be simpler than they really are. On the other hand, by avoiding theory and presenting for example the more complicated alternating-current

formulae as purely empirical results the author must have made them appear rather formidable. How much better would they be understood and remembered if deduced from the vector theory!

For readers grounded in physics and mathematics, however, the chapters which follow on radiophysics proper will be of considerable value, especially perhaps those on measuring methods, roentgen diagnostic procedures, the properties of films and intensifying screens etc. The radiotherapeutic chapter seems to be less satisfying, very little being said for instance about the techniques of radium treatment and the planning of dosage through several different portals in order to obtain the distribution desired.

A European reader will find that the matter, quite naturally, refers mainly to American conditions, and will miss many things in common use this side of the Atlantic. Thus, the only condenser chamber described is the Victoreen r-meter, and Sievert is not even mentioned.

Each chapter is concluded by a list containing many useful references. It is to be regretted, however, that the number of references added since the first edition of 1941 is so small.

Sven Benner.

A STUDENT'S RADIOLOGICAL MATHEMATICS. By L. A. W. Kemp. xii + 315 pages. Blackwell Scientific Publications, Ltd, Oxford, 1951. 21 sh.

This book covers a course of simple mathematics as applied to radiology, beginning from the first elements of algebra. The application of geometry to the formation of the roentgen image and especially body section radiography, to foreign body localization, radium dose calculations and other radiologic problems is followed by chapters on trigonometric functions, logarithms and the slide-rule. The graphical representation of various functions and the construction and use of nomograms with straight parallel scales are also described. Three appendices contain the elements of differential and integral calculus, questions from British radiologic examinations and certain numeric constants, formulae etc.

The treatment is, throughout the book, clear and easily followed even by readers with little previous mathematic knowledge. Numerous examples and exercises, mostly chosen from radiologic applications, serve well to eludicate the subject matter further. In a book of this type, certain approximations in the interest of simplification are certainly necessary, but the reviewer feels the author has sometimes gone a little too far in this direction. Thus, in the chapter on body section radiography, only plane structures parallel to the film are considered. The shape and size of the shadow of a structure in space certainly changes as the radiation source moves, even though the movement be parallel to the film.

These are, however only matters of detail and, as a whole, the book can warmly be recommended to those in need of a refresher course in simple mathematics. It should also be useful to teachers in radiology.

Sven Benner.